exposure on lag 0 compared to other single-day lags reported by Kim et al. (2012). The observed risks were generally greater in magnitude for multiday lags (i.e., lag 0−1) compared to single-day lags (i.e., lag 0, lag 1). Similar results were observed for studies investigating short-term $PM_{2.5}$ exposure and heart failure (Talbott et al., 2014; Haley et al., 2009; Stieb et al., 2009), though Kim et al. (2012) observed positive associations for delayed lags (single day lags 2, 3, and 4) and a negative association for Lag day 0. Among recent studies evaluating the relationship between short-term $PM_{2.5}$ exposure and OHCA, authors generally observed the strongest associations for immediate lag periods (Ensor et al., 2013; Rosenthal et al., 2013; Dennekamp et al., 2010; Silverman et al., 2010), though some found delayed associations days (Wichmann et al., 2013).

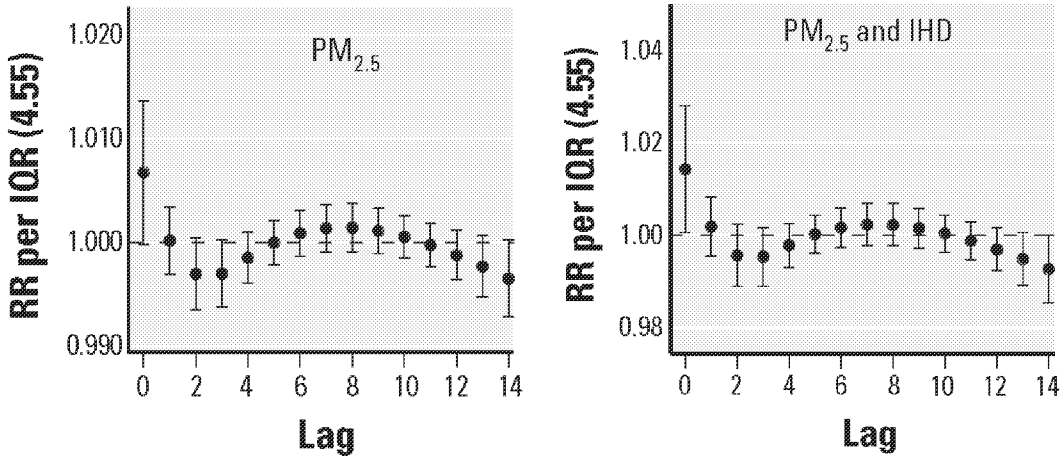


Figure 6-13 Pattern of RRs for single day lags 0−14 for aggregate cardiovascular disease (CVD) hospitalizations (left) and IHD hospitalizations (right) reported by Kim et al. (2012).

Most of the studies that examined multiple lag periods reported no evidence of a positive association between short-term $PM_{2.5}$ exposure and hospital admissions and ED visits for CBVD at any of the lag periods evaluated (Qiu et al., 2013; Kim et al., 2012; O'Donnell et al., 2011; Haley et al., 2009). However, when evaluating specific stroke subtypes, Lisabeth et al. (2008) and Wing et al. (2015) observed positive associations between $PM_{2.5}$ concentrations and ischemic stroke for immediate Lag days (lags 0 or 1), but not for delayed lags (single day lags 2, 3,4, 5). Limited evidence was inconsistent when comparing different lag periods in studies of ED visits and hospital admissions for arrhythmia. Talbott et al. (2014) reported positive associations for immediate lag periods (lag 0, 1, 0−1) with stronger associations observed for multiday lags compared to single-day lags. In contrast, Haley et al. (2009) observed negative associations for both immediate (i.e., 0,1) and delayed (i.e., 2, 3,4) single day lags in their evaluation of arrhythmia ED visits.

Recent multicity studies of short-term $PM_{2.5}$ exposure and cardiovascular mortality have conducted extensive examinations of the lag structure of associations. Of these studies, some only examined single-day lags (Lippmann et al., 2013c) or multi-day lags (Milojevic et al., 2014), while a few examined multi-day lags aimed at specifically addressing whether there is evidence of an immediate (lag 0–1 days), delayed (lag 2–5 days), or prolonged (lag 0–5 days) effect of $PM_{2.5}$ on cardiovascular mortality. Several studies provide evidence of an immediate $PM_{2.5}$ effect on cardiovascular mortality with associations largest in magnitude at lag 0 (Stafoggia et al., 2017; Janssen et al., 2013; Lippmann et al., 2013c; Samoli et al., 2013). Lanzinger et al. (2016a) and Samoli et al. (2013) provide some evidence indicating the potential for stronger associations with short-term $PM_{2.5}$ exposure averaged over delayed (e.g., lag 2–5) and prolonged (e.g., lag 0–5) lag periods and CVD mortality. Overall, recent multicity studies that examined the lag structure of associations, generally support the immediate effect of $PM_{2.5}$ on cardiovascular mortality, but also provide some evidence that associations may exist for exposures averaged over longer durations. However, the initial studies examining multi-day lags providing evidence of a delayed or prolonged effect are not supported when examining a series of single-day lags over the same duration.

Additionally, few studies examined subdaily averaging times, or exposures averaged over one or multiple hours during Lag day 0. In Rochester, New York, Gardner et al. (2014) observed positive associations between STEMI and $PM_{2.5}$ at lags of 0 hours and 0–2 hours, with evidence of positive associations for multi-hours lags up to 24 hours. Several studies investigating OHCA also examined subdaily averaging times, and generally observed positive associations, though the associations were consistently higher in magnitude for daily lags (single and multiday lags 0–4) compared to the subdaily lags (Straney et al., 2014; Ensor et al., 2013; Rosenthal et al., 2013). For example, Ensor et al. (2013) observed a small increase in risk of OHCA consistent with an increase in $PM_{2.5}$ concentrations in the hour preceding the OHCA event (1.84% [95% CI: −2.16, 5.90%]), but a larger magnitude association corresponding to an increase in 2-day moving average $PM_{2.5}$ (6.58% [95% CI: 0.83, 12.64%]). Wellenius et al. (2012a) considered subdaily averaging times when evaluating CBVD endpoints and observed positive associations for ischemic stroke at hourly lags ranging from 0 to 26 hours, with the largest magnitude of associations for lags from 8 to 20 hours. Overall, these evaluation of subdaily lags provide additional support for the immediate effect of short-term $PM_{2.5}$ exposure on cardiovascular hospital admissions, ED visits, and mortality.

In summary, there is evidence to support an immediate effect of short-term $PM_{2.5}$ exposure on hospital admissions and ED visits for aggregate CVD outcomes, IHD, HF and OHCA, as well as for cardiovascular mortality. This evidence comes from the evaluation of both single-day and multiday lags, as well as studies that evaluated subdaily lag periods. In contrast, the evidence was less consistent across studies, as well as across different lag periods within the same study, for associations between short-term $PM_{2.5}$ exposure and hospital admissions and ED visits for CBVD or arrhythmia. Overall, stronger associations were observed for immediate lags for most CVD outcomes, and the associations tended to be

stronger for immediate multiday lag periods (i.e., 0–1, 0–2) compared to immediate single-day lag periods (i.e., 0, 1).

6.1.15 Associations between $PM_{2.5}$ Components and Sources and Cardiovascular Effects

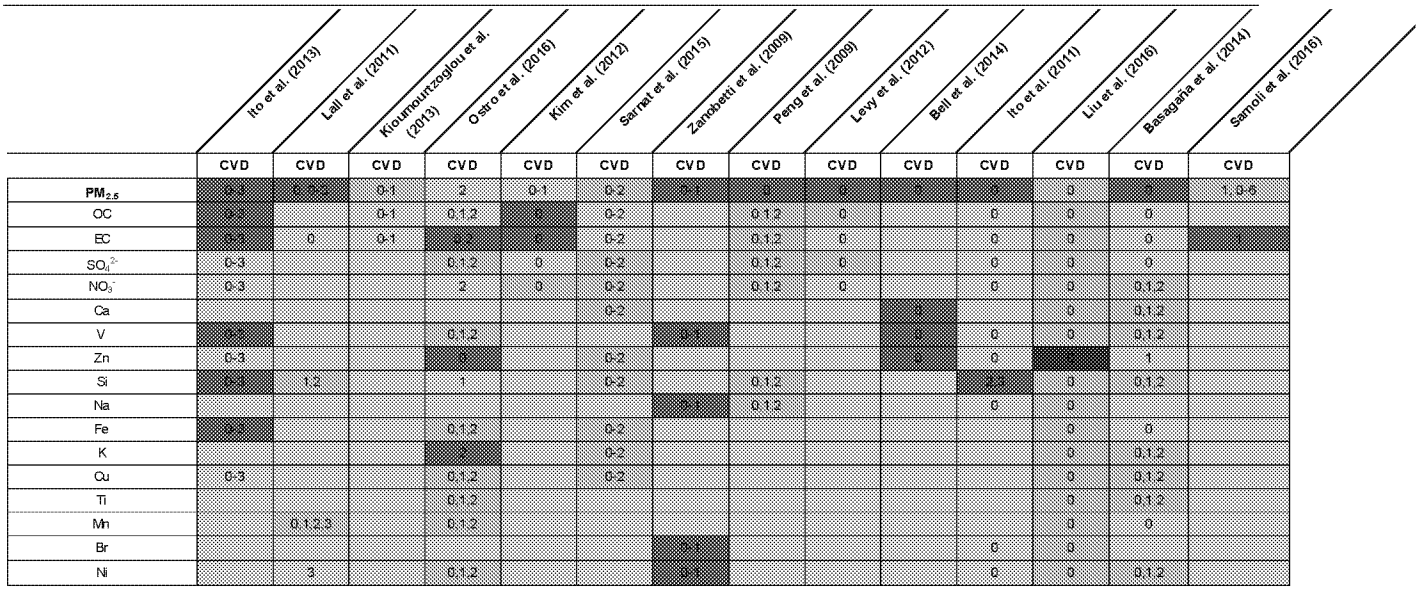
While many PM components are associated with a range of health effects, the 2009 PM ISA concluded that there was not sufficient evidence to differentiate between the PM components or sources that more closely related to health effects than $PM_{2.5}$ mass (U.S. EPA, 2009). However, there was some evidence for associations between increases in cardiovascular effects (e.g., hospital admissions and cardiovascular mortality) with sulfate particles and EC. In addition, several PM sources (i.e., crustal/soil/road dust and traffic) were associated with increased cardiovascular mortality and ST-segment changes. Generally, studies evaluated in the 2009 PM ISA that evaluated individual PM components and sources observed inconsistent results, with no apparent trend or pattern of effect across $PM_{2.5}$ components or across CVD endpoints.

Numerous recent studies examine short-term exposure to $PM_{2.5}$ sources or components and cardiovascular effects and the results are generally consistent with those reported in the 2009 PM ISA. To clearly illustrate the uncertainty in attributing cardiovascular effects to individual $PM_{2.5}$ components or sources versus $PM_{2.5}$ mass, this section is organized by component or source and discussed in the context of associations with $PM_{2.5}$ mass. In cases where studies examined short-term exposure to a $PM_{2.5}$ component or source and any cardiovascular health outcome, the evidence for the relationship is evaluated and synthesized below. This allows for integration across cardiovascular health endpoints in the evaluation of $PM_{2.5}$ components and sources. In each case, the evidence for the $PM_{2.5}$ component or source was evaluated in the context of the available evidence for the relationship with $PM_{2.5}$ mass.

The examination of the relationship between $PM_{2.5}$ components and CVD can generally be divided into two types of analyses: (1) those that examine whether specific components modify the $PM_{2.5}$-cardiovascular effects association, or (2) those that examine whether an individual component is associated with cardiovascular effects and potentially a better indicator of PM toxicity compared to PM mass. Although approach 1 is considered one of the techniques used to assess component toxicity as detailed in Mostofsky et al. (2012), these studies are often used to examine heterogeneity in $PM_{2.5}$-CVD risk estimates. As a result, the focus of this section is on those techniques that fall under approach 2, which includes assessing $PM_{2.5}$ component effect by component concentration or component concentration adjusted for $PM_{2.5}$ mass. Other techniques identified by Mostofsky et al. (2012) that would fall under approach 2 (i.e., component residual or $PM_{2.5}$ residual) were not used in the evaluation of $PM_{2.5}$ components and CVD health effects.

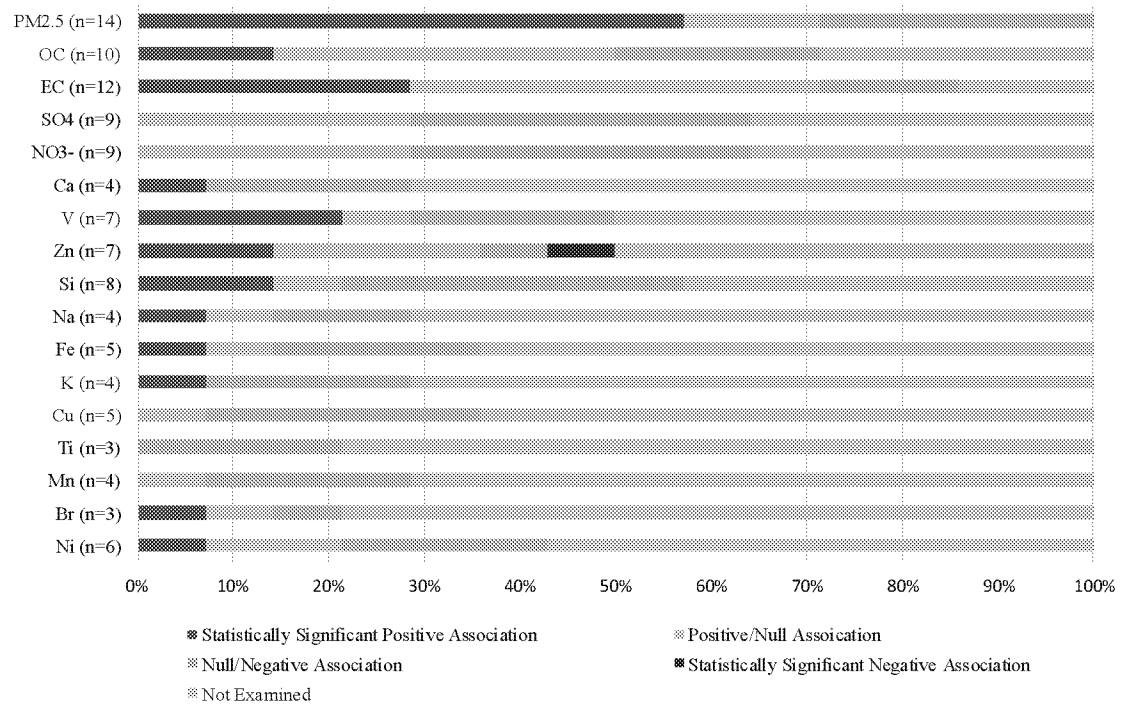
Taking this approach, the evidence does not demonstrate an individual PM component or source that is more consistently associated with CVD health endpoints. The largest body of evidence examining

the association with $PM_{2.5}$ components is for ED visits or hospital admissions for aggregate CVD, and these results are summarized in Figure 6-14 and Figure 6-15. Figure 6-14 provides a snapshot of the evidence from studies of aggregate CVD ED visits and hospital admissions that evaluated associations with both $PM_{2.5}$ and $PM_{2.5}$ components. The evidence varies among components, with some studies finding positive associations between almost all $PM_{2.5}$ components evaluated and various cardiovascular health outcomes. The figure demonstrates the most consistent, positive associations with $PM_{2.5}$ mass, though similar patterns of associations are observed with EC, OC and, though evaluated in fewer studies, several metals (e.g., V, Zn, Si, Ni). Overall, associations with aggregate CVD ED visits and hospital admissions are not more clearly linked to a particular $PM_{2.5}$ component compared with $PM_{2.5}$ mass, and within-study comparisons do not show a consistent difference in association between $PM_{2.5}$ mass and a particular component (Figure 6-14). While the number of studies is more limited for other CVD endpoints (e.g., cause-specific ED visits and hospital admissions, measures of blood pressure, HRV, vascular function, and biomarkers of inflammation and oxidative stress), similar trends in associations are observed within and across studies evaluating these endpoints. Several sources of uncertainty common among studies of $PM_{2.5}$ components and sources limit their ability to contribute to causal inference. These include measurement error due to spatiotemporal heterogeneity and poorly addressed potential confounding by other components in the $PM_{2.5}$ mixture. The evidence for $PM_{2.5}$ components and sources is detailed below.



Note: Cells represent associations examined for studies of $PM_{2.5}$ mass and $PM_{2.5}$ components and aggregated cardiovascular hospital admissions or emergency department visits. Numbers within cells represent lag(s) at which association was observed. Dark blue = statistically significant positive association; light blue = positive association; light orange = null or negative association; red = statistically significant negative association; grey = component not examined. Only $PM_{2.5}$ components for which there were at least three studies available were included in the table. $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 µm, OC = organic carbon, EC = elemental carbon, SO_4^{2-} = sulfate, NO_3^- = nitrate.

Figure 6-14 Heat map of associations observed between short-term $PM_{2.5}$ and $PM_{2.5}$ component exposure and hospital admissions and emergency department visits for cardiovascular-related effects.



Note: Bars represent the percent of associations across studies for $PM_{2.5}$ mass or $PM_{2.5}$ components for aggregated cardiovascular hospital admissions and emergency room visits where dark blue = statistically significantly positive, light blue = positive, light orange = null/negative, red = statistically significantly negative, and grey hatch = not examined. N = number of studies that provided an estimate. $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 μm, OC = organic carbon, EC = elemental carbon, SO_4^{2-} = sulfate, NO_3^- = nitrate.

Figure 6-15 Distribution of associations for hospital admissions and emergency department visits for cardiovascular-related effects and short-term $PM_{2.5}$ and $PM_{2.5}$ components exposure in studies detailed in Figure 6-14.

6.1.15.1 Elemental and Black Carbon

In coronary artery disease patients in Boston, MA similar negative associations were observed between $PM_{2.5}$ and BC with rMSSD for 30-minute up to 5-day exposures (Zanobetti et al., 2010). Negative associations were also observed for HF, although associations were stronger for BC than $PM_{2.5}$ with averaging times from 2−5 days. No associations were observed in this panel for $PM_{2.5}$ exposures with SDNN, but BC exposures from 30-minutes up to 2-hours were reduced (Zanobetti et al., 2010). Associations were similar for BC and $PM_{2.5}$ in studies conducted with panels having pre-existing cardiovascular disease as Schneider et al. (2010) and Bartell et al. (2013) observed negative associations between BC and $PM_{2.5}$ with pNN50 and rMSSD, or HRV, respectively. Finally, Weichenthal et al. (2014a), in a quasi-experimental study that included women cycling on high and low traffic routes for 2-hours, found that associations between SDNN, LF, and LF/HF were similarly positive for both $PM_{2.5}$

and BC. However, negative associations observed between $PM_{2.5}$ and rMSSD and pNN50 were not observed for BC.

Several studies examined associations between measures of vascular function and ambient BC concentrations in addition to $PM_{2.5}$. While Madrigano et al. (2010) reported positive associations between VCAM-1 and BC that were not observed for $PM_{2.5}$, other studies did not find associations between BC and VCAM-1 or other biomarkers of vascular function including VEGF, ICAM-1, and ET-1 (Wilker et al., 2011; Liu et al., 2009). Ljungman et al. (2014) report evidence for associations between BC and pulse wave amplitude for 2 to 5-day averages in the Framingham Heart Study, which was consistent with results for $PM_{2.5}$.

In a quasi-experimental study conducted by Strak et al. (2013a), associations were null for fibrinogen and platelet counts with $PM_{2.5}$ and BC; however, positive associations were reported between $PM_{2.5}$ and vWF that were not observed for BC. Conversely, substantial reductions in lag time in FXII-mediated (intrinsic) thrombin generation were associated with BC exposures but not $PM_{2.5}$ exposures (Strak et al., 2013b). Croft et al. (2017) and Chen et al. (2017) also examined associations between BC and biomarkers related to coagulation in panels of adults with pre-existing cardiovascular conditions and observed positive associations between BC and fibrinogen and 12-hour up to 3-day lagged exposures; although associations with $PM_{2.5}$ were only observed by Croft et al. (2017) and 1−24 hour lags. Associations were not observed for D-dimer or vWF in these studies.

In a panel study including 31 young, healthy adults exposed to air pollution at five different sites with intermittent exercise, Steenhof et al. (2014) reported mixed results for associations between EC and WBC counts measured 2 and 18 hours post-exposure, though patterns in associations were very similar to those for $PM_{2.5}$. More specifically, positive associations were observed for WBC counts, neutrophils 2 hours post-exposure, and monocytes 18 hours post-exposure. In this same panel, positive associations were observed for both $PM_{2.5}$ and EC, but the magnitude of effect was smaller for EC (Strak et al., 2013a).

Liu et al. (2009) did not find evidence for associations between 24-hour outdoor BC or personal measurements of $PM_{2.5}$ and biomarkers for inflammation or oxidative stress (i.e., IL6, TNF-α, TBARS, 8-isoprostane) in a panel of older adults residing in retirement communities. Similar results were observed in studies conducted by Wittkopp et al. (2013) and Chen et al. (2017) in panels of adults with coronary artery disease or having risk factors for CVD as null associations were observed for CRP and up to 5-day averages of EC or 3-day lags for BC. In contrast, Croft et al. (2017) reported positive associations for CRP and 12 and 24-hour lags of BC, although negative associations were observed with myeloperoxidase, a marker for neutrophil activity.

6.1.15.2 Organic Carbon

In contrast with previous studies, recent studies generally support an association of OC with CVD-related hospital admissions, ED visits, cardiovascular function metrics (e.g., HRV), and biomarkers of inflammation (e.g., WBC, CRP). Due to the relatively few studies, it is difficult to judge the consistency of recent results for any one CVD endpoint. That said, the consistency and magnitude of CVD effect associations generally are similar for OC and $PM_{2.5}$ (Figure 6-14 and Figure 6-15), which are in line with the large contribution of OC to total $PM_{2.5}$ mass (Section 2.4.4).

Like $PM_{2.5}$, OC was associated with CVD-related ED visits and hospital admissions in locations across U.S. regions. One of the most informative studies is an extensive analysis of Medicare beneficiaries in 64 cities, which found CVD hospital admissions were associated with OC, particularly during the cold season at lag 0 (Ito et al., 2013). While these associations were strongest at lag 0 in the cold season, OC showed associations present at longer lag periods; however, no individual component had stronger associations than $PM_{2.5}$ mass. A study in Denver, CO reported that $PM_{2.5}$ concentrations of OC were associated with hospital admissions for IHD and aggregate CVD (Kim et al., 2012). On the other hand, in Denver, CO Kim et al. (2012) did not observe a positive association between OC and CBVD hospital admissions. Sarnat et al. (2015) observed a positive association between ED visits for heart failure and $PM_{2.5}$ OC content in the St. Louis, MO metropolitan area. A study of eight California counties found a small positive association with CVD hospital admissions and vehicle-related $PM_{2.5}$ and OC.

A recent study evaluated HRV metrics and exposure to OC in patients with IHD in Erfurt, Germany; an increase in 24-hour exposure to OC was associated with decreases in HF, rMSSD, and pNN50; similar associations were observed for $PM_{2.5}$ with the exception of the association with HF (Schneider et al., 2010). In addition, a number of studies observed positive associations between OC exposure and biomarkers of coagulation and inflammation. In a quasi-experimental study conducted in Utrecht, the Netherlands, OC was associated with fibrinogen, platelet counts, and vWF (Strak et al., 2013a), while associations were only observed between $PM_{2.5}$ and vWF in this study. Chen et al. (2017) did not observe associations between fibrinogen and OC or $PM_{2.5}$, but positive associations were reported for D-dimer and OC with 1 and 2-day lagged exposures. In a recent panel study, Steenhof et al. (2014) reported mixed results for associations between OC and WBC counts measured 2 and 18 hours post-exposure, though patterns in associations were generally similar to those for $PM_{2.5}$. More specifically, positive associations were observed for WBC counts and monocytes 18 hours post-exposure, though OC was associated with lymphocytes and not neutrophils in contrast to $PM_{2.5}$. In this same panel, positive associations were observed for both $PM_{2.5}$ and OC, but the magnitude of effect was larger for OC (Strak et al., 2013a). Wittkopp et al. (2013) and Chen et al. (2017) examined OC in a panel of older adults and those with risk factors for cardiovascular disease, respectively, and did not find evidence for associations with CRP, although Wittkopp et al. (2013) did find positive associations with soluble receptor for IL6 that were not observed for $PM_{2.5}$.

6.1.15.3 Secondary $PM_{2.5}$—Sulfate, Nitrate, Ammonium

Several recent studies add to the limited supporting evidence in the 2009 PM ISA for associations of sulfate (SO_4^{2-}), nitrate (NO_3^-), and ammonium (NH_4^+) with CVD ED visits and hospital admissions, though the evidence is not entirely consistent. Evidence for effects on other CVD outcomes is limited. In most locations, results are similar between $PM_{2.5}$ and sulfate and nitrate in direction and magnitude of association.

An analysis of Medicare data across 119 U.S. counties found that nitrates from $PM_{2.5}$ were associated with CVD hospital admissions (Levy et al., 2012), and Peng et al. (2009) observed a similar pattern in the same population over a slightly shorter time period. Similarly, Sarnat et al. (2015) observed that ED visits for IHD were positively associated with $PM_{2.5}$ nitrates in St. Louis, MO. In 4 cities in southern Europe, Basagaña et al. (2015) reported positive associations with sulfate from $PM_{2.5}$. In contrast, studies in Denver (Kim et al., 2012), Houston (Liu et al., 2016b) and California (Ostro et al., 2016) reported that $PM_{2.5}$ concentrations of sulfates and nitrates were not associated with aggregate CVD hospital admissions. Using data for transmural myocardial infarctions in the NJ MIDAS registry, Rich et al. (2010) observed the largest effects on the days with the highest tertile of sulfate, nitrate, and ammonium, and the lowest tertile of elemental carbon. The authors interpreted their findings as indicating that $PM_{2.5}$ on days with pollution mixtures that are formed through atmospheric chemistry and depleted in primary $PM_{2.5}$ pollutants were most strongly associated with transmural infarctions.

Evidence for associations between sulfate or nitrate and other CVD endpoints is more limited, but generally positive. Despite reporting a generally null association between $PM_{2.5}$ and ICD activations, Anderson et al. (2010) observed a positive association between SO_4^{2-} and atrial fibrillation in London, England. Strak et al. (2013a) examined associations between sulfate and nitrate with fibrinogen, platelet counts, and vWF. Positive associations were observed for both nitrate and sulfate with fibrinogen, though associations with $PM_{2.5}$ were null. In contrast, $PM_{2.5}$ and sulfate were positively associated with vWF, but associations with nitrate were null. In addition, the extrinsic coagulation pathway was positively associated with nitrate and sulfate, but null for $PM_{2.5}$ (Strak et al., 2013b).

6.1.15.4 Metals

Compared with $PM_{2.5}$ mass, short-term increases in ambient concentrations of metals are inconsistently associated with CVD ED visits and hospital admissions. In the expanded body of recent studies, none observed associations with a metal but not $PM_{2.5}$ mass (Figure 6-15). Most studies observed an association with some metal, and studies that examined numerous metals often observed an association with multiple metals. However, findings are inconsistent for any individual metal or the sum of metals.

Among Medicare beneficiaries in Connecticut and Massachusetts, Bell et al. (2014) found that $PM_{2.5}$ from Ca, Zn, and V were positively associated with CVD hospital admissions. In an additional

study of Medicare beneficiaries in 64 cities, CVD hospital admissions were associated with copper, iron, selenium, silicon, and zinc (Ito et al., 2013). No individual component had stronger associations than $PM_{2.5}$ mass. In separate analyses of hospital admissions (Liu et al., 2016b) and ED visits (Liu et al., 2016a) in Houston, TX authors reported positive associations between stroke and bromine, nickel (ED visits) and As (hospital admissions), but observed negative associations for zinc, calcium, iron, potassium, manganese, vanadium, (ED visits), and potassium, (hospital admissions). Sarnat et al. (2015) reported that ED visits for IHD were negatively associated with 24-hour concentrations of $PM_{2.5}$ Fe and Si concentrations in St. Louis, MO while CVD hospital admissions were negatively associated with Si concentrations. A study of eight California counties (Ostro et al., 2016) found a small positive association with potassium, and zinc, while Basagaña et al. (2015) reported positive associations with Zn, Fe, and Mn from $PM_{2.5}$ in 4 cities in southern Europe.

In Atlanta, GA Suh et al. (2011) observed that $PM_{2.5}$ transition metals were associated with CVD, and specifically IHD, hospital admissions. Similarly, in New York City, NY Ito et al. (2011) found that most of the $PM_{2.5}$ chemical components considered were associated with CVD hospital admissions, making it difficult to draw conclusions about specific components.

Ambient concentrations of metals can be spatiotemporally more heterogeneous than $PM_{2.5}$ total mass, and thus, exposure measurement error could contribute to inconsistent findings for metals. Another uncertainty not addressed in the evidence is whether metals are independently associated with CVD effects as gaseous pollutants were not examined and correlations with gases and other $PM_{2.5}$ components were generally not reported.

6.1.15.5 Other $PM_{2.5}$ components

New information links cardiovascular effects with cyclohexanes and hopanes, though information is available from few studies and locations for each. In a combined analysis from Atlanta, GA Birmingham, AL and Dallas, TX Kioumourtzoglou et al. (2013) observed that cyclohexane concentrations, a marker of gasoline exhaust, were associated with higher rates of IHD and heart failure. Sarnat et al. (2015) observed a positive association between ED visits for heart failure and hopanes in the St. Louis, MO metropolitan area, though Kioumourtzoglou et al. (2013) reported null associations with hopanes.

6.1.15.6 Sources of $PM_{2.5}$

Several recent studies apportioned $PM_{2.5}$ components into source factors and provide some evidence linking $PM_{2.5}$ from traffic to cardiovascular hospital admissions. Studies of CVD hospital admissions are note entirely consistent, but provide some evidence for an association with $PM_{2.5}$

concentration during wildfires. Evidence is generally sparse for $PM_{2.5}$ from dust or soil, oil, salt, and local industry.

Some studies have attempted to identify specific sources or components of $PM_{2.5}$ that may be most strongly associated with hospital admissions or ED visits for CVD. Cardiovascular hospital admissions were associated with $PM_{2.5}$ from motor vehicles or traffic in various U.S. regions. In New York City, NY Lall et al. (2011) found that IHD, heart failure, and cerebrovascular disease hospital admissions were associated with $PM_{2.5}$ from traffic, but not other $PM_{2.5}$ components. In a subsequent analysis in the same data set, Lall et al. (2011) found that $PM_{2.5}$ derived from traffic was associated with same-day rates of hospital admissions for CVD while $PM_{2.5}$ from soil was inversely related. A study of eight California counties found small, positive associations with hospital admissions for IHD, heart failure, and arrhythmia and vehicle- or soil-related $PM_{2.5}$ in addition to $PM_{2.5}$ mass (Ostro et al., 2016). In source-based analyses Ito et al. (2013) reported an association with the traffic category during the cold season and CVD hospital admissions. Another large, multicity Medicare study also found that CVD hospitalizations were strongly related to $PM_{2.5}$ components from traffic sources, as well as sea salt/street salt, industrial combustions, and soil and road sources (Zanobetti et al., 2009). A study of Medicare beneficiaries by Zanobetti et al. (2009) noted stronger associations with MI and $PM_{2.5}$ from traffic, industrial combustion sources, sea salt/street salt, industrial sources, and wood burning and soil. Ostro et al. (2016) also examined $PM_{2.5}$ in relation to MI, and though they reported no association with $PM_{2.5}$ mass, they did report small positive associations with vehicle and soil related $PM_{2.5}$.

Examination of wildfire-related $PM_{2.5}$ was available from different regions across the U.S. In the 2009 PM ISA Delfino et al. (2009a) reported positive associations of total CVD admissions, IHD, CHF, and CBVD with southern California wildfires during 2003. Smaller studies reported inconsistent evidence of associations across outcomes. A study during a month of Colorado wildfires in 2012 reported generally null associations for all CVD outcomes except IHD (Alman et al., 2016). Conversely, a small study in Albuquerque, NM reported positive associations with total CVD admissions, CBVD, and PVD during a 2011 wildfire (Resnick et al., 2015). Additionally, two small studies of rural North Carolina peat wildfire events reported positive associations with hypertension and all-cause cardiac outcomes (Tinling et al., 2016) and CHF (Rappold et al., 2012; Rappold et al., 2011). In a large study of 561 urban and rural counties in the western U.S. using Medicare data Liu et al. (2017) reported null associations between total CVD HA/ED visits on wildfire smoke days compared to nonsmoke days from 2004−2009. This study is notable for the ability to incorporate a large number of rural counties into the analysis by using modeled wildfire-specific $PM_{2.5}$ data; however, the use of dichotomous exposure to define smoke and nonsmoke days may be source of exposure misclassification, even in sensitivity analyses. Furthermore, though wildfires are generally regional events, the use of county level exposure assignment may contribute to exposure misclassification particularly among large, rural western counties. Overall, evidence is limited for any association between exposure to wildfire derived $PM_{2.5}$ and cardiovascular HA/ED visits. Variability in study results may be related to regional heterogeneity in wildfire characteristics that depend on fuel sources, ecology, and meteorological conditions.

6.1.15.7 Associations Between $PM_{2.5}$ Components and Sources and Effects in People with Diabetes

Associations of short-term exposure BC with increases in inflammatory markers and HOMA-IR (Brook et al., 2016; O'Neill et al., 2007), decreased HRV and BAD (Table 6-32). Sulfate was associated with circulating markers of inflammation but not with BAD, FMD or NMD. OC was negatively associated with BAD (Zanobetti et al., 2014b). The single study that considered copollutant confounding reported that the association between BC and HRV did not persist after adjustment for NO_2 or CO.

Table 6-32 Summary of studies evaluating short-term exposure to $PM_{2.5}$ components and sources in people with diabetes.

Study	Study Population	Exposure Assessment	Concentration	Outcome	Copollutants Examined
(O'Neill et al., 2007) Boston, MA 1998–2002	N = 92 RCT participants Type 2 diabetes	24-h avg 1 monitor within 1.5 km of clinic	BC Mean (SD): 1.1 (0.8) IQR 0.6	ICAM-1 VCAM-1 vWF	NR
†(Brook et al., 2016) Beijing, China BC	Adults with metabolic syndrome	24-h avg, lag 1–7 day, 3 monitors	BC Mean (SD) 6.5 (3.7) IQR 4.5	HOMA-IR	NR
†(Sun et al., 2015) Shanghai, China 2010	N = 53 Type 2 diabetes	4-h moving avg prior to clinic visit, monitor near residence (April, June, Sept)	BC Mean (SD): 4.09 (2.37)	SDNN	Correlations (*r*): PNC5–560 = 0.52 2-pollutant models decreased after adjustment for Ozone Increased/null after adjustment for NO_2 and CO
†(Zanobetti et al., 2014b) Boston, MA 2006–2010 Five follow-up exams 2 weeks apart	N = 64 49–54 yr Type 2 diabetes	24 h avg, 1 monitor, reside within 25 km 1 and 5-day avg concentrations	BC Mean 0.61 Median 0.54 IQR 0.35	BAD FMD NMD	Correlations (*r*): $PM_{2.5}$ = 0.65, OC = 0.50, PN = −0.05, SO_4 = 0.52
†(Zanobetti et al., 2014b) Boston, MA 2006–2010 Five follow-up exams 2 weeks apart	N = 64 49–54 yr Type 2 diabetes	24 h avg, 1 monitor, reside within 25 km 1 and 5-day avg concentrations	OC Mean 3.03 Median 2.85 IQR 1.75	BAD FMD NMD	Correlations (*r*): $PM_{2.5}$ = 0.54, BC = 0.50, PN = −0.15, SO_4 = 0.48

Table 6-32 (Continued): Summary of studies evaluating short-term exposure to $PM_{2.5}$ components and sources in people with diabetes.

†(Zanobetti et al., 2014b) Boston, MA 2006–2010 Five follow-up exams 2 weeks apart	N = 64 49–54 yr Type 2 diabetes	24 h avg, 1 monitor, reside within 25 km 1 and 5-day avg concentrations	Sulfate Mean 2.13 Median 1.61 IQR 1.47	BAD FMD NMD	Correlations (*r*): $PM_{2.5}$ = 0.76, BC = 0.52, PN = −0.27, OC = 0.43
†(O'Neill et al., 2007) Boston, MA 1998–2002	N = 92 RCT participants Type 2 diabetes	24-h avg 1 monitor within 1.5 km of clinic	Sulfate Mean (SD): 3.0 (2.0) IQR 2.2	ICAM-1 VCAM-1 vWF	NR

BAD = Brachial Artery Diameter; FMD = Flow Mediated Dilation; NR = Not Reported; NDM = Nitroglycerin Mediated Dilation; SDNN = Standard Deviation of NN intervals; rMSSD = Root Mean Square of the Successive Differences between adjacent NNs; ICAM-1 = intercellular adhesion molecule-1; VCAM-1 = vascular cell adhesion molecule-1; vWF = Von Willebrand factor; MPO = myeloperoxidase; hs CRP = high sensitivity c-reactive protein; IL-6 = interleukin 6

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6.1.15.8 Toxicology Studies of Individual Components and Sources as Part of the PM Mixture

2 It is still not known whether particular sources or components of $PM_{2.5}$ are responsible for health
3 effects or if certain sources and components can be ruled out as not contributing to adverse health effects.
4 At the time of the last PM NAAQS review, the ISA concluded that "many constituents of PM can be
5 linked with differing health effects and the evidence is not yet sufficient to allow differentiation of those
6 constituents or sources that are more closely related to health outcomes" (U.S. EPA, 2009). The following
7 section is organized by health endpoint and exposure duration and includes in vivo toxicology studies
8 where animals were exposed via inhalation. Lippmann et al. (2013b) conducted a series of studies where
9 $ApoE^{-/-}$ mice were exposed to $PM_{2.5}$ CAPs for six hours/day, five days/week for a total of six months
10 (NPACT Study 1). Separate studies were conducted in Manhattan, NY, Tuxedo, NY, East Lansing, MI,
11 Seattle, WA and Irvine, CA that began in 2007 with the last one concluding in 2011. At all locations,
12 mice were exposed to CAPs at nominal 8–10 times ambient concentrations, resulting in mean exposure
13 concentrations of 138 $\mu g/m^3$ at Irvine, 136 $\mu g/m^3$ at Tuxedo, 122.9 $\mu g/m^3$ at Manhattan, 67.8 $\mu g/m^3$ at
14 East Lansing and 60.5 $\mu g/m^3$ at Seattle. Measured $PM_{2.5}$ components included for source apportionment
15 were Al, Ba, Br, Ca, Cu, Fe, K, Mn, Ni, Pb, S, Se, Si, V, Zn, and EC. In addition, NO_2 data were used for
16 the Manhattan analysis to aid in the identification and separation of a traffic source category. Acute CAPs
17 exposure resulted in some changes in HR and HRV measurements. Generally, the most significant effects
18 were observed for mice exposed to $PM_{2.5}$ from either site in NY, with decreases in HR and LF/HF and
19 increases in SDNN and rMSSD at lag 0 and 1 (and to a lesser extent at lag 2) in animals exposed to
20 Manhattan $PM_{2.5}$. For Tuxedo, the pattern was opposite, with significant increases in HR and LF/HF and
21 significant decreases in SDNN and rMSSD at lag 0 (and to a lesser extent at lag 1 and 2). Very few
22 significant changes in heart rate variability parameters were observed in animals exposed to $PM_{2.5}$ in East
23 Lansing, Seattle or Irvine.

The number of significant changes in HR and HRV by site at Lag day 0 were analyzed for 16 individual components. Across all of the sites, the greatest number of HR/HRV changes were for Na (149), Br (144) and Si (138). As mentioned previously, Manhattan and Tuxedo had double the number of HR/HRV changes compared to East Lansing, Seattle or Irvine. For Manhattan, the greatest number of HR/HRV changes was for Ni and *P* (both with 68) followed by Na (65), V (59), S (54) and EC (50). The pattern was different for Tuxedo, as the greatest number of HR/HRV changes was associated with Br (49), *P* (46), S (43) and K (42). The fewest number of HR/HRV changes across all sites was for Cr (31), Pb (40), Cu (57) and Mn (59).

Embedded within the NPACT study, a subset of data and results were provided in in Chen et al. (2010). This subset focused on the Manhattan and Tuxedo (aka Sterling Forest) exposures and HR and HRV changes. ApoE$^{-/-}$ mice were exposed for 6 months to filtered air or $PM_{2.5}$ CAPs from May to September 2007. Mean CAPs concentrations in Manhattan were identical to those reported in Lippmann et al. (2013b) of 122.9 μg/m^3 and slightly higher than those reported in Lippmann et al. (2013b) of 133.3 μg/m^3 in Sterling Forest. As expected, the changes in HR and HRV parameters with CAPs concentration were similar to the NPACT study. Decreases in HR and LF/HF and increases in SDNN, rMSSD, LF and HF were observed with mice exposed to Manhattan CAPs at all time periods (9 AM–2 PM, 7 PM–10 PM, 1 AM–4 AM) for lags 0 and 1. At Sterling Forest, increases in HR and decreases in SDNN, rMSSD, LF, and HF were observed at lag 0 and select periods at lag 1. When examining 20 individual elements with HR and HRV responses, Br, EC, Na, Ni, *P*, S, and V consistently resulted in significant changes across all time periods (magnitude and directions not provided) on lags 0 and 1 at the Manhattan site. Al and Se were associated with significant changes at lag 1 only and Ni and *P* were associated with significant changes at lag 2. At the Sterling Forest site, only S was associated with significant changes at lag 0, with Br and Zn at lag 1, and only Si for lags 0 and 1.

Two pollutant regression models were also performed using CAPs, S or EC as one factor and individual components as the second factor. For animals exposed to Manhattan CAPs, the CAPs associations were more strongly associated with altered cardiac function compared to the majority of elements for lag 0 and 1. Ni and S demonstrated stronger associations with ECG changes compared to other elements at lag 0. For animals exposed to Sterling Forest CAPs, the CAPs association were also stronger than those for the other elements at lag 0. Individual elements Br, S, Si, and Zn were more strongly associated at lag 1 and lag 2 compared to other elements.

In a study conducted for 13 consecutive days (8 hr/day) in summer 2005 and winter 2006 in southwest Detroit, MI, ECG changes were assessed in male SH rats exposed to $PM_{2.5}$ CAPS (Rohr et al.). Mean concentration of CAPS during the summer exposure was 518 μg/m^3, with mean exposure concentrations in the winter being 357 μg/m^3. PM composition was much more variable in summer compared to winter. Over the entire 8-hour exposure period in summer, significant differences in HR, SDNN or rMSSD were not observed between air controls and CAPs-exposed animals. When 30-minute intervals were examined during summer exposures, reductions in SDNN were associated with EC, Fe, Sr,

Mg, As, Ca, Ti, Mn, Se, Ba, Sb, Pb, Ce and Zn. Over the entire 8-hour period in winter, only HR demonstrated significant responses. Increased HR was associated with Mg and decreased HR was associated with Fe, Ti, Cu, Pb, Sn, Co, EC, OC, Se and In. For 30-minute intervals in winter, both HR and rMSSD were significantly different between the air and CAPs exposed groups. Generally, HR was decreased in the PM-exposed animals and rMSSD was increased. Reductions in HR were associated with Ba, As, Tb, EC, Cd, Zn, S, Sr, Mn, Ca, Ti, Fe, Rb, Cr, Mg, Se, Sb, K and Cu; only La had an association with increased HR. Increases in rMSSD were associated with Ba, EC, Zn, As and Rb.

In a study with similar methods to (Rohr et al., 2011), male SH rats were exposed to $PM_{2.5}$ CAPs from Steubenville, OH for 13 consecutive days (8 hr/day) in August 2006 (Kamal et al., 2011). During exposure, winds originated from the southwest (SW) or northeast (NE). Mean CAPs concentration over the exposure period was 406 $\mu g/m^3$. Approximately 30 $PM_{2.5}$ components were identified and used in univariate regression to connect to ECG changes. Furthermore, PMF was used to determine the major emission sources contributing the $PM_{2.5}$ concentrations during the study period. Sulfate and OC made up over 50% of CAPs mass. Using 30-minute average data over the entire exposure period (regardless of wind direction), significant CAPs effects were observed for HR and SDNN, but not rMSSD. When separating out wind direction, HR and SDNN changes were significant for both the SW and NE wind directions, whereas rMSSD changes were only significant for the SW wind direction. Generally, decreases in HR were observed with wind originating from the NE and associated with S, Se, Pb, Rb, Mn, Zn, Sr, Fe, Cd. In contrast, increases in HR were observed with wind originating from the SW and associated with Mo, La, PM mass, Ce, V, Ti, As and Sb. For SDNN, the majority of changes were decreases with more components associated when winds were from the NE (Sb, Pb, Zn, Rb, As, Sn, K, V, Cd, Mo, Ti, Cr). Fewer components were associated with decreased SDNN with winds from the SE (Mo, As, Sb). Changes in rMSSD were only observed with wind from the SW direction, with both increases (Al, Mg) and decreases noted (Mo, V). To assess the contribution of $PM_{2.5}$ grouped components on resultant health effects in toxicological studies, we used the approach from (Stanek et al., 2011). This approach is consistent with the Review Panel of the NPACT initiative that states both source categories and component concentrations should be used directly in the health analyses (assuming the study design permits) with a focus on examining consistencies and differences between the two approaches (Lippmann et al., 2013b). Four criteria were applied to the studies that were identified during the literature search. Each study needed to meet all of the criteria in order to be included:

- exposures conducted using $PM_{2.5}$ from U.S. airsheds or those representative of the U.S. (e.g., Europe, Canada);
- inclusion of at least five PM components;
- grouping of PM components using statistical methods, for which the groups were not predefined based on common physical or chemical properties (e.g., water soluble vs. nonsoluble); and
- formal statistical analysis investigating the relationship between groups of PM components or PM sources and health effects.

Studies of that examined $PM_{2.5}$ using individual components or individual source emissions are not included, as this is a limited approach that does not consider the combined contribution of the $PM_{2.5}$ mixture to health effects.

In the NPACT Study 1 (Lippmann et al., 2013b), a source characterization statistical model was used to determine associations between identified source categories and the HR and HRV changes.

Table 6-33 shows general HR and HRV results over the exposure period for each location and identified source category. This is a semi-quantitative evaluation of the number of significant associations, given that there were 6 cardiac measures (HR, SDNN, rMSSD, LF, HF, and LF/HF) analyzed over 4 different time periods (9 AM–2 PM, 7 PM–10 PM, 10 PM–1 AM, 1 AM–3 AM) and 3 different lags (0, 1 and 2).

Table 6-33 NPACT study results for identified source categories and occurrence of heart rate (HR) and heart rate variability (HRV) changes.

Location	Identified Source Categories	General HR and HRV Results
Manhattan, NY	Incineration (Pb, Zn); Steel (Fe, Mn); Soil (Al, Si, Ca); Residual oil combustion (Ni, V); Sulfur-coal (S, Se); Fireworks (K, Ba, Cr); Salt (Na, Mg, Cl); Traffic (EC, NO_2); Secondary aerosols (S, OC)	Residual oil combustion had the largest number of HR/HRV changes (54); combining sulfur-coal and secondary aerosol source categories to represent regionally transported $PM_{2.5}$ had even greater number of responses (59); salt and traffic demonstrated changes (48 and 44, respectively); changes associated with soil were less frequent (13); for steel and incineration, the strongest associations were on lag 0 with little response on lag 1 or 2
Tuxedo, NY	Sulfur-coal (Se, S, *P*, Br); Soil (Si, Ti, Al, Ca); Salt (Na, Cl); Ni refinery (Fe, Ni, Zn, Ca, Mn, V)	Sulfur-coal had the most number of HR/HRV changes (27), with soil having the second most (24); soil had most number of responses on lag 1 (18); almost all salt significant associations were on lag 0 (13 of 14)
East Lansing, MI	Soil (Si, Ca, Al, Fe); Sulfur-coal (S); Residual oil combustion (V, Ni); Zn-Cl (Zn, Cl); EC-OC (EC, OC)	Overall much fewer instances of significant HR/HRV associations compared to other sites (20 total across all source categories); soil and Zn-Cl had the most number of HR/HRV changes (6 each), although greatest soil associations were observed with lag 2; the most number of sulfur-coal associations were observed at lag 0 (4); little associations with OC-EC and residual oil combustion (2 and 1, respectively)

Table 6-33 (Continued): NPACT study results for identified source categories and occurrence of heart rate (HR) and heart rate variability (HRV) changes.

Location	Identified Source Categories	General HR and HRV Results
Seattle, WA	Salt (Na, Mg, Cl); Soil (Al, Si, Ca, Fe); Traffic and road dust (Ca, Mn, Cu, Fe, Zn, EC); Biomass combustion (K, Cu, EC); Residual oil combustion (V, Ni); Sulfates (S, Br)	Soil had the most HR/HRV changes (31) across all lags; residual oil combustion and salt had second and third most responses (13 and 8, respectively) with both demonstrating more changes at lag 2; biomass combustion was only associated with HR/HRV changes on lag 0 (6) and sulfates only associated with HR/HRV changes on lag 2 (5)
Irvine, CA	Residual oil combustion (V, Ni); Soil (Si, Al); Traffic (Mn, Cu, Ca, EC); Biomass combustion (K, EC); Salt (Cl, K); Metals (Pb, Zn)	Soil had the most number of significant HR/HRV changes (20), with most observed on lag 2 (14); a similar temporal relationship was demonstrated with biomass combustion (11 total, with 6 on lag 2); residual oil combustion was third (10) distributed evenly across the lags; soil, metals and traffic had much fewer significant associations with HR/HRV changes (5, 4, and 3, respectively)

As expected, those locations with greater $PM_{2.5}$ responses, also demonstrated more counts of significant associations between source categories and HR and HRV measurements, albeit all locations had at least one source category strongly associated with a change in cardiac function.

Looking across locations and source categories, soil was associated with HR/HRV changes in mice exposed to $PM_{2.5}$ at any location, with the greatest frequencies occurring on lag 1 or 2. Residual oil combustion was most frequently associated with HR/HRV changes in Manhattan across all lags and was also frequently observed in Seattle and Irvine, albeit to a greater extent on lags 1 and 2 in Seattle. There was a much greater frequency of HR/HRV changes related to traffic in Manhattan compared to Seattle and Irvine, which is likely explained by the fact that the laboratory in Manhattan is located in close proximity to busy roads. The source categories of secondary aerosols in Manhattan, sulfur-coal in Tuxedo and East Lansing, and sulfates in Seattle were all associated with HR/HRV changes. However, the frequency of these changes were less than other source categories, with the exception of Tuxedo (where concentrations were much higher than Seattle or East Lansing). In Manhattan, Tuxedo, Seattle and Irvine, salt was also associated with HR/HRV changes, with frequency of occurrence being in the middle of the range of all source categories at each location; the timing of the associations (i.e., lag) varied by location. Biomass combustion was associated with HR/HRV changes only in Seattle and Irvine, with the association only being observed at lag 0 in Seattle.

6.1.16 Summary and Causality Determination

A large body of recent evidence confirms and extends the evidence from the 2009 PM ISA (U.S. EPA, 2009) indicating that there is a causal relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects. The strongest evidence in the 2009 PM ISA was from epidemiologic studies of ED visits and hospital admissions for IHD and HF, with supporting evidence from epidemiologic studies of cardiovascular mortality. Changes in various measures of cardiovascular function in CHE studies provided some biological plausibility for these associations. In addition, animal toxicological studies reporting some evidence of reduced myocardial blood flow during ischemia, altered vascular reactivity, and ST segment depression provided additional biological plausibility. In the current review, evidence supporting the causal determination includes generally positive associations reported from epidemiologic studies of hospital admissions and ED visits for cardiovascular-related effects, and in particular, for IHD and HF. Results from these observational studies are supported by experimental evidence from CHE and animal toxicological studies of endothelial dysfunction, as well as endpoints indicating impaired cardiac function, increased risk of arrhythmia, changes in HRV, increases in BP, and increases in indicators of systemic inflammation, oxidative stress, and coagulation. Additional results from observational panel studies, though not entirely consistent, provide at least some evidence of increased risk of arrhythmia, decreases in HRV, increases in BP, and ST segment depression. Thus, epidemiologic panel studies also provide some support to the causal determination and to biological plausibility. Finally, epidemiologic studies of CVD-related mortality provide additional evidence that demonstrates a continuum of effects from biomarkers of inflammation and coagulation, subclinical endpoints (e.g., HRV, BP, endothelial dysfunction), ED visits and hospital admissions, and eventually death. The current body of evidence also reduces uncertainties from the previous review related to potential copollutant confounding and limited biological plausibility for CVD effects following short-term $PM_{2.5}$ exposure. Evidence supporting the causal determination for short-term $PM_{2.5}$ exposure and cardiovascular effects reached in this ISA is discussed below and summarized in Table 6-34, using the framework for causal determination described in the Preamble to the ISAs (U.S. EPA, 2015).

The generally consistent, positive associations observed in numerous epidemiologic studies of ED visits and hospital admissions for IHD, HF and combined cardiovascular-related endpoints contribute to the evidence supporting a causal relationship between short-term $PM_{2.5}$ exposure and CVD. Among this body of evidence, nationwide studies of older adults using Medicare reported positive associations between $PM_{2.5}$ concentrations and HF hospital admissions (Section 6.1.3.1). Consistent with the results of these large Medicare studies, additional multicity studies conducted in the northeast reported positive associations between short-term $PM_{2.5}$ concentrations and ED visits or hospital admissions for IHD (Sections 6.1.2.1), while studies conducted in the U.S. and Canada reported positive associations between short-term $PM_{2.5}$ concentrations and ED visits for HF. Results from epidemiologic studies conducted in single cities contribute additional support to the causal determination, but are less consistent, showing both positive and null associations between $PM_{2.5}$ concentrations and these endpoints (Section 6.1.2 and Section 6.1.3). When considered as a whole, the recent body of IHD and HF epidemiologic evidence is in

agreement with evidence from previous ISAs reporting mainly positive associations between short-term $PM_{2.5}$ concentrations and ED visits and hospital admissions. In addition, a number of more recent CHE, animal toxicological, and epidemiologic panel studies provide evidence that $PM_{2.5}$ exposure could plausibly result in IHD or HF through pathways that include endothelial dysfunction, arterial thrombosis, and arrhythmia (Section 6.1.1). Also supporting the plausibility for IHD and HF endpoints are more recent epidemiologic panel studies reporting some evidence of ST segment depression (Section 6.1.2.2) and a recent CHE study and animal toxicological study showing decreased cardiac function following short-term $PM_{2.5}$ exposure (Section 6.1.3.2 and Section 6.1.3.3).

Results from additional CHE studies published since the last review also support a causal relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects. The most consistent evidence from these studies is for endothelial dysfunction as measured by changes in BAD or FMD. More specifically, in contrast to the last review where a single study did not find changes in endothelial function, all but one of the studies in the current review examining the potential for endothelial dysfunction reported an effect of $PM_{2.5}$ on measures of blood flow (Section 6.1.13.2) relative to FA exposure. That being said, all studies were not in agreement with respect to the timing of the effect or the mechanism by which reduced blood flow was occurring (i.e., endothelial independent vs. endothelial dependent mechanisms). In addition to endothelial dysfunction, CHE studies using CAPs, but not filtered DE generally reported evidence for small increases in blood pressure, although there were inconsistencies across studies with respect to changes in SBP and DBP. It is notable however, that in CAPs studies where increases in one measure of BP (e.g., SBP), but not the other (e.g., DBP) was found to be statistically significant, that other measure of BP usually changed as well, but the change was not found to be statistically significant (Section 6.1.6.3). In addition, although not entirely consistent, there is also some evidence across CHE studies for conduction abnormalities/arrhythmia (Section 6.1.4.3), changes in HRV (Section 6.1.10.2), changes in hemostasis that could promote clot formation (Section 6.1.12.2), and increases in inflammatory cells and markers (Section 6.1.11.2). Thus, when taken as a whole, CHE studies are in coherence with epidemiologic studies by demonstrating that short-term exposure to $PM_{2.5}$ may result in the types of cardiovascular endpoints that could lead to ED visits and hospital admissions.

Animal toxicological studies published since the 2009 PM ISA also support a causal relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects. A recent study demonstrating decreased cardiac contractility and left ventricular pressure in mice is coherent with the results of epidemiologic studies reporting associations between short-term $PM_{2.5}$ exposure and HF (Section 6.1.3.3). In addition, similar to CHE studies, there is generally consistent evidence in animal toxicological studies for indicators of endothelial dysfunction (Section 6.1.13.3). Studies in animals also provide evidence for changes in a number of other cardiovascular endpoints following short-term $PM_{2.5}$ exposure. Although not entirely consistent, these studies provide at least some evidence of conduction abnormalities and arrhythmia (Section 6.1.4.4), changes in HRV (Section 0), changes in BP (Section 6.1.6.4), and evidence for systemic inflammation and oxidative stress (Section 6.1.11.3). Finally, these toxicological studies also

suggest that genetic background, diet, and PM composition may influence the effect of short-term $PM_{2.5}$ exposure on some of these health endpoints.

As outlined above, across the scientific disciplines there is evidence for a continuum of cardiovascular-related health effects following short-term exposure to $PM_{2.5}$. These effects range from relatively modest increases in biomarkers related to inflammation and coagulation, to subclinical CVD endpoints such as endothelial dysfunction, to ED visits and hospital admissions for outcomes such as IHD and HF. In coherence with this continuum of effects is a body of epidemiologic studies reporting a relatively consistent relationship between short-term $PM_{2.5}$ exposure and CVD-related mortality. These epidemiologic studies also reduce a key uncertainty from the last review by providing evidence that gaseous pollutants are not likely to confound the $PM_{2.5}$-cardiovascular mortality relationship.

Taken together, the recent evidence described throughout Section 6.1 extends the consistency and coherence of the evidence base reported in the 2009 PM ISA and 2004 AQCD. Direct evidence for $PM_{2.5}$ exposure-related cardiovascular effects can be found in a number of CHE and animal toxicological studies. In coherence with these results are epidemiologic panel studies also finding that $PM_{2.5}$ exposure is associated with some of the same cardiovascular endpoints reported in CHE and animal toxicological studies. There is a limited number of studies evaluating some of these endpoints, and there are some inconsistencies in results across some of these animal toxicological, CHE and epidemiologic panel studies, though this may be due to substantial differences in study design, study populations, or differences in PM composition across air sheds. That being said, the results from these epidemiologic panel, CHE, and animal toxicological studies, in particular those related to endothelial dysfunction, impaired cardiac function, ST segment depression, thrombosis, conduction abnormalities, and BP provide coherence and biological plausibility for the consistent results from epidemiologic studies observing positive associations between short-term $PM_{2.5}$ concentrations and IHD and HF, and ultimately cardiovascular mortality. Overall, considering the entire evidence base, there continues to be sufficient evidence to conclude that **a causal relationship exists between short-term $PM_{2.5}$ exposure and cardiovascular effects.**

Table 6-34 Summary of evidence for a causal relationship between short-term $PM_{2.5}$ exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high quality studies at relevant $PM_{2.5}$ concentrations	Increases in ED visits and hospital admissions for IHD and CHF in multicity studies conducted in the U.S., Canada, Europe, and Asia Increases in cardiovascular mortality in multicity studies conducted in the U.S., Canada, Europe, and Asia.	Section 6.1.2.1 Section 6.1.3.1 Section 6.1.9	5.8–18.6 µg/m^3 5.8–18.0 µg/m^3
Consistent evidence from controlled human exposure studies at relevant $PM_{2.5}$ concentrations	Consistent changes in measures of endothelial dysfunction Generally consistent evidence for small increases in measures of blood pressure following CAPs exposure Additional evidence of conduction abnormalities, heart rate variability, impaired heart function, systemic inflammation/oxidative stress	Section 6.1.13.2 Section 6.1.6.3 Section 6.1.4.3 Section 6.1.3.2 Section 6.1.10.2 Section 6.1.11.2	24–325 µg/m^3 See Tables in identified sections
Consistent evidence from animal toxicological studies at relevant $PM_{2.5}$ concentrations	Consistent changes in indicators of endothelial dysfunction. Additional evidence of changes in impaired heart function, conduction abnormalities/arrhythmia, heart rate variability, blood pressure, systemic inflammation/oxidative stress	Section 6.1.13.3 Section 6.1.6.4 Section 6.1.4.4 Section 6.1.3.3 Section 0 Section 6.1.11.3	168.7–510 µg/m^3 See Tables in identified sections
Epidemiologic evidence from copollutant models provides some support for an independent $PM_{2.5}$ association	The magnitude of $PM_{2.5}$ associations remain positive, but in some cases are reduced with larger confidence intervals in copollutant models with gaseous pollutants. Further support from copollutant analyses indicating positive associations for cardiovascular mortality. Recent studies that examined potential copollutant confounding are limited to studies conducted in Europe and Asia. When reported, correlations with gaseous copollutants were primarily in the low to moderate range ($r < 0.7$).	Section 6.1.14.1	
Consistent positive epidemiologic evidence for associations between $PM_{2.5}$ exposure and CVD ED visits and hospital admissions across exposure measurement metrics	Positive associations consistently observed across studies that used ground-based (i.e., monitors), model (e.g., CMAQ, dispersion models) and remote sensing (e.g., AOD measurements from satellites) methods, including hybrid methods that combine two or more of these methods.	Kloog et al. (2014)	

Table 6-34 (Continued): Summary of evidence indicating that a causal relationship exists between short-term $PM_{2.5}$ exposure and cardiovascular effects.

Rationale for Causal Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Generally consistent evidence for biological plausibility of cardiovascular effects	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to short-term $PM_{2.5}$ exposure. Includes evidence for reduced myocardial blood flow, altered vascular reactivity, and ST segment depression.	Section 6.1.1 Figure 6-1	
Uncertainty regarding geographic heterogeneity in $PM_{2.5}$ associations	Multicity U.S. studies demonstrate city-to-city and regional heterogeneity in $PM_{2.5}$-CVD ED visit and hospital admission associations. Evidence supports that a combination of factors including composition and exposure factors may contribute to the observed heterogeneity.	Section 6.1.2.1 Section 6.1.3.1	

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

6.2 Long-Term $PM_{2.5}$ Exposure and Cardiovascular Effects

The scientific evidence pertaining to the cardiovascular health effects of $PM_{2.5}$ reviewed in the 2009 PM ISA was "sufficient to infer a causal relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects" (U.S. EPA, 2009). The strongest line of evidence comprised findings from several large U.S. cohort studies that consistently showed positive associations between $PM_{2.5}$ exposure and cardiovascular mortality (Krewski et al., 2009; Miller et al., 2007; Laden et al., 2006; Pope III et al., 2004). While several studies included in the 2009 ISA for PM reported associations of long-term PM_{10} exposure with morbidity outcomes such as post-MI congestive heart failure (CHF) (Zanobetti and Schwartz, 2007) and deep vein thrombosis (DVT) (Baccarelli et al., 2008), epidemiologic evidence relating to $PM_{2.5}$ was limited to a study of postmenopausal women (Miller et al., 2007) and cross-sectional analyses of self-reported cardiovascular effects among participants in the German Heinz Nixdorf Recall (HNR) study (Hoffmann et al., 2009; Hoffmann et al., 2006). These studies reported associations with coronary heart disease (CHD) and stroke. Biological plausibility and coherence with the epidemiologic findings were provided by studies using genetic mouse models of atherosclerosis demonstrating enhanced atherosclerotic plaque development and inflammation following 4 to 6-month exposures to $PM_{2.5}$ CAPs (U.S. EPA, 2009). Evidence from a limited number of toxicological studies in

mice reporting CAPs-induced effects on coagulation factors, hypertension and vascular reactivity was also drawn upon to support the causal conclusion. Recent epidemiologic studies add to the already strong evidence base supporting the association of long-term exposure to $PM_{2.5}$ with cardiovascular mortality (Section 6.2.10). Associations between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity outcomes (i.e., IHD, stroke) were observed in some studies with the most consistent results in people with preexisting diseases (CHAPTER 12). Additional experimental studies of long-term exposure to $PM_{2.5}$ CAPs add to the collective evidence available to support a direct effect of $PM_{2.5}$ on the cardiovascular system, and provide biological plausibility for associations observed in epidemiologic studies.

Some uncertainties remained to be addressed at the completion of the 2009 PM ISA despite the strong evidence supporting a causal relationship between long-term exposure to $PM_{2.5}$ and cardiovascular effects. The following sections provide an evaluation of the most policy relevant scientific evidence, focusing on the extent to which recently available studies further characterize the relationship between long-term exposure to $PM_{2.5}$ and cardiovascular effects. Specifically, the current section focuses on studies where long-term average $PM_{2.5}$ concentrations are less than 20 $\mu g/m^3$ whereas the epidemiologic studies supporting the causal conclusion in the 2009 ISA were generally conducted in urban areas where mean $PM_{2.5}$ concentrations ranged up to 29.0 $\mu g/m^3$. In addition, an expanded set of longitudinal epidemiologic analyses that is currently available to assess the effect of long-term exposure to $PM_{2.5}$ on the incidence of cardiovascular disease and to examine temporal changes in specific endpoints such as coronary artery calcium (CAC), markers of systemic inflammation and coagulation. A more extensive literature on CAPs exposure reduces uncertainties related to inclusion of diesel and other mixture studies in the 2009 PM ISA. These studies, in combination with a limited number of recently available epidemiologic analyses that examine copollutant confounding, strengthen the evidence for a direct effect of long-term $PM_{2.5}$ on the cardiovascular system. Finally, an expanded set of studies describing the shape of the C-*R* function across the range of $PM_{2.5}$ concentrations is available and studies that use spatiotemporal exposure models to characterize exposure to populations that may be at greater distance from air monitors add to the collective evidence in the current review.

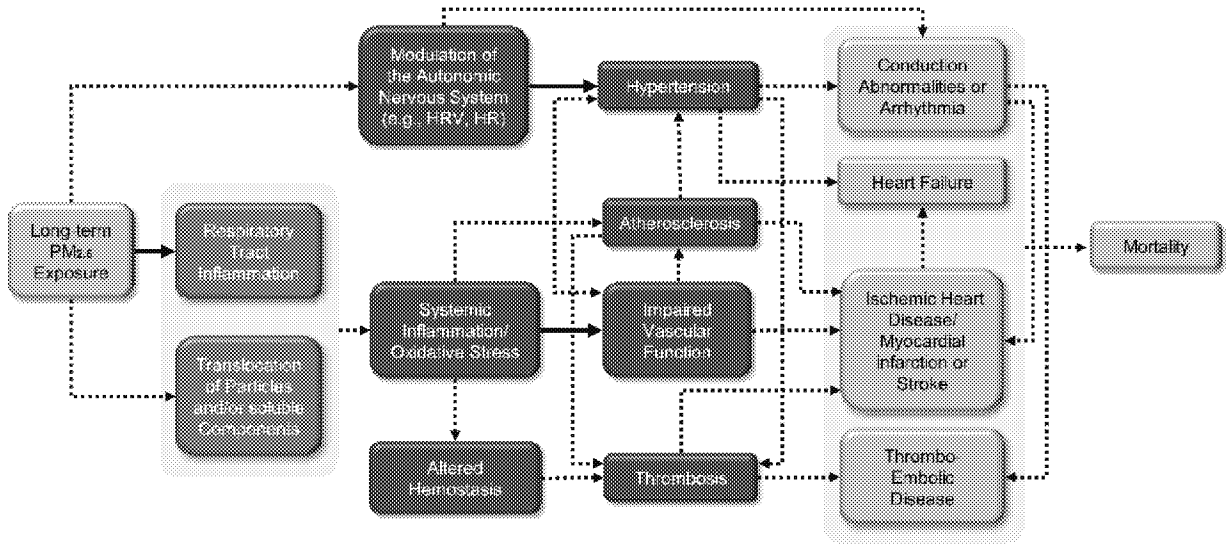
The subsections below provide an evaluation of the most policy relevant scientific evidence relating-long-tern $PM_{2.5}$ exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following long-tern $PM_{2.5}$ exposure (Section 6.2.1). Following this discussion, the health evidence relating long-tern $PM_{2.5}$ exposure and specific cardiovascular health outcomes is discussed in detail: ischemic heart disease and myocardial infarction (Section 6.2.2), cerebrovascular disease and stroke (Section 6.2.3), atherosclerosis (Section 6.2.4) heart failure and impaired heart function (Section 6.2.5) cardiac electrophysiology and arrhythmia (Section 6.2.6), blood pressure and hypertension (Section 6.2.7), peripheral vascular disease (PVD), venous thromboembolism and pulmonary embolisms (Section 6.2.8), aggregated cardiovascular outcomes (Section 6.2.9), and cardiovascular-related mortality (Section 6.2.10). The evidence for an effect of $PM_{2.5}$ exposures on endpoints such as changes in heart rate variability (HRV) and endothelial function are discussed (Section 6.2.11, Section 6.2.12, Section 6.2.13,

and, Section 6.2.14), as are copollutant confounding (Section 0), shape of the concentration response function (Section 6.2.16), and the relationship between health effects and exposure to specific $PM_{2.5}$ components (Section 6.2.17). Finally, the collective body of evidence is integrated across and within scientific disciplines[62], and the rationale for the causality determination is outlined in Section 6.2.18.

6.2.1 Biological Plausibility

This subsection describes the biological pathways that potentially underlie cardiovascular health effects resulting from long-term inhalation exposure to $PM_{2.5}$. Figure 6-16 graphically depicts these proposed pathways as a continuum of pathophysiological responses—connected by arrows—that may ultimately lead to the apical cardiovascular events observed in long-term epidemiologic studies. This discussion of "how" long-term exposure to $PM_{2.5}$ may lead to these cardiovascular events also provides biological plausibility for the epidemiologic results reported later in Section 6.2. In addition, most studies cited in this subsection are discussed in greater detail throughout Section 6.2.

[62] As detailed in the Preface, risk estimates are for a 5 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations unless otherwise noted.



Note: the boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below

Figure 6-16 Potential biological pathways for cardiovascular effects following long-term exposure to $PM_{2.5}$.

When considering the available health evidence, plausible pathways connecting long-term exposure to $PM_{2.5}$ to the apical events reported in epidemiologic studies are proposed in Figure 6-16. The first proposed pathway begins as respiratory tract inflammation leading to systemic inflammation[63]. The second proposed pathway involves modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that long-term exposure to $PM_{2.5}$ may result in a series of pathophysiological responses that could lead to cardiovascular events such as IHD and HF.

Long-term inhalation exposure to $PM_{2.5}$ may result in respiratory tract inflammation and oxidative stress (Section 5.2). Inflammatory mediators such as cytokines produced in the respiratory tract have the potential to enter into the circulatory system where they may cause distal pathophysiological responses that could lead to overt cardiovascular disease. For example, following long-term exposure to $PM_{2.5}$, Kampfrath et al. (2011) reported that vascular dysfunction occurred via NADPH oxidase and inflammatory pathways that required toll like receptor 4 (TLR4). In addition, release of inflammatory

[63] It is also possible that particles ~200 nm or less, or soluble particle components can translocate directly into the circulatory system (Chapter 4) and lead to systemic inflammation, although the extent to which particle translocation occurs remains unclear.

mediators into the circulation such as monocyte chemoattractant protein 1 (MCP-1) can result in the recruitment of additional inflammatory cells, and thus amplify the initial inflammatory response (Carr et al., 1994). Thus, it is important to note that there is evidence from long-term experimental studies in animals (Tanwar et al., 2017; Aztatzi-Aguilar et al., 2015; Gorr et al., 2014; Lippmann et al., 2013a; Ying et al., 2013; Deiuliis et al., 2012; Wold et al., 2012; Kampfrath et al., 2011) demonstrating an increase in inflammatory cells, cytokines, or oxidative stress markers in the circulatory system following long-term $PM_{2.5}$ exposure. The release of cytokines such as IL-6 into the circulation can stimulate the liver to release inflammatory proteins and coagulation factors that can alter hemostasis and increase the potential for thrombosis (Lucking et al., 2011; van Eeden et al., 2005). Evidence from several $PM_{2.5}$ epidemiologic studies identified an association between long-term exposure to $PM_{2.5}$ and coagulation factor and/or liver derived inflammatory markers (e.g., CRP) in the blood (Hajat et al., 2015; Viehmann et al., 2015; Hennig et al., 2014; Ostro et al., 2014). These observed effects may alter the balance between pro and anticoagulation proteins and therefore, increase the potential for thrombosis, which may then promote IHD, stroke, or thromboembolic disease elsewhere in the body. Systemic inflammation has also been shown to induce impaired vascular function (Kampfrath et al., 2011)—a systemic pathological condition characterized by the altered production of vasoconstrictors and vasodilators—that over time promotes plaque formation leading to atherosclerosis. Specifically, vascular dysfunction is often accompanied by endothelial cell expression of adhesion molecules and release of chemo attractants for inflammatory cells. Macrophages may then internalize circulating lipids leading to the formation of foam cells: a hallmark of atherosclerotic lesions that may increase in size with $PM_{2.5}$ exposure, particularly in the presence of genetic and dietary risk factors (Rao et al.; Lippmann et al., 2013a). Over time, these atherosclerotic lesions may become calcified as evidenced in a longitudinal epidemiologic study of $PM_{2.5}$ (Kaufman et al., 2016), and this often leads to arteriole stiffening and promotion of IHD or stroke. Importantly, evidence for impaired vascular function in response to long-term exposure to $PM_{2.5}$ is found in animal experimental studies (Ying et al., 2015; Kampfrath et al., 2011; Sun et al.).

In addition to long-term $PM_{2.5}$ exposure leading to cardiovascular disease through inflammatory pathways, there is also evidence that exposure to $PM_{2.5}$ could lead to cardiovascular disease through modulation of the autonomic nervous system. That being said, the mechanism by which long-term exposure to $PM_{2.5}$ results in autonomic nervous system modulation remains unclear. Nonetheless, there is evidence from studies in animals demonstrating modulation of autonomic function (as evidenced by changes in HRV and/or HR) following long-term $PM_{2.5}$ exposure (Ying et al.; Lippmann et al., 2013a; Wold et al., 2012). Moreover, there is also evidence for an increase in BP (Aztatzi-Aguilar et al., 2016; Ying et al., 2015; Wold et al., 2012) in animals following long-term $PM_{2.5}$ exposure. These results are consistent with associations reported in epidemiologic studies between long-term exposure to $PM_{2.5}$ and increases in BP and hypertension (Zhang et al., 2016; Chen et al., 2014a). This is important given that hypertension can lead to HF through cardiac remodeling that results in reduced pumping efficiency (Santos et al, 2014). Similarly, hypertension can contribute to impaired vascular function and atherosclerosis (Brook et al., 2010a), which as noted above, may lead to IHD. Hypertension may also result in arrhythmia through cardiac remodeling (Cascio, 2016; Brook et al., 2010a). Thus, it is

noteworthy that there is epidemiologic evidence of associations between long-term exposure to $PM_{2.5}$ and indicators of potential arrhythmia (Van Hee et al., 2011). Arrhythmia can also contribute to IHD and stroke. For example, atrial fibrillation (a type of arrhythmia) is characterized by blood pooling and potentially clotting in the upper chamber (atria) of the heart. These clots can ultimately be pumped out of the heart and lodged in arteries supplying the brain with oxygen, thereby resulting in a stroke. Studies of hypertension and arrhythmia therefore provide additional plausibility for epidemiologic studies finding associations between long-term exposure to $PM_{2.5}$ and IHD, HF, stroke, and ultimately mortality.

When considering the available evidence, there are plausible pathways connecting long-term exposure to $PM_{2.5}$ to cardiovascular health effects. The first proposed pathway begins with respiratory tract injury and inflammation that may enter into the circulatory system potentially inducing a series of pathophysiological responses that could ultimately result in IHD, stroke, HF, or thromboembolic disease elsewhere in the body (Figure 6-16). The second proposed pathway involves changes in the autonomic nervous system that may result in hypertension, arrhythmia, and potentially the same apical events (Figure 6-16). Taken together, these proposed pathways provide biological plausibility for epidemiologic results of cardiovascular health effects and will be used to inform a causal determination, which is discussed later in the chapter (Section 0).

6.2.2 Ischemic Heart Disease and Myocardial Infarction

The terms ischemic heart disease (IHD) coronary artery disease (CAD) or coronary heart disease (CHD) are generally interchangeable as they appear in the epidemiologic literature on the effects of air pollution. The majority of IHD is caused by atherosclerosis (Section 6.2.4), which can result in the blockage of the coronary arteries and restriction of blood flow to the heart muscle. A myocardial infarction (MI) or heart attack is an acute event that results in heart muscle tissue death secondary to coronary artery occlusion. Studies that examine the ability of short-term exposure to $PM_{2.5}$ to trigger an MI are discussed in Section 6.1.2 whereas the studies examining the effect of long-term exposure on the incidence of MI or IHD are discussed here (Section 6.2.2).

The literature examining the association of long-term exposure to $PM_{2.5}$ with IHDs has expanded substantially from the few studies available for inclusion in the 2009 PM ISA. Overall, findings from recent epidemiologic studies do not provide entirely consistent evidence of an association between long-term exposure to $PM_{2.5}$ and IHD in the populations studied. The strongest evidence of an association with IHD, however, is found in populations with pre-existing diseases (CHAPTER 12).

6.2.2.1 Epidemiologic Studies

This section evaluates the epidemiologic studies reporting associations of long-term exposure to $PM_{2.5}$ with the development, prevalence or recurrence of IHDs including MI (Table 6-35).

Table 6-35 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and ischemic heart disease.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
Miller et al. (2007) 36 metro areas, U.S. Prospective cohort $PM_{2.5}$: 2000 Follow-up: 1994–1998	WHI observational cohort N = 65,893 Median follow-up: 6 yr	Annual avg of closest monitor (2000) Most women within 10 km of monitor	Median 13.4 IQR 11.6–18.3	MI and CHD Medical record review by physician adjudicators	Copollutant model: NR Copollutant correlations: NR
†Hart et al. (2015b) U.S. (contiguous states) Prospective cohort $PM_{2.5}$: 1989–2006 Follow-up: 1988–2006	NHS N = 114,537 Follow-up: ~16 yr	Annual avg at residential address, spatiotemporal model with monthly surface $PM_{2.5}$ measurements; (C-V R2 0.76 and 0.77 pre- (limited $PM_{2.5}$ data) and post-1999, respectively) See Yanosky et al. (2009) for details	Mean (1989–2006): 13.4 (SD:3.3) Mean: 2000–2006: 12 (SD: 2.8)	Self-reported physician diagnosed IHD with medical record review	Copollutant models: NR Copollutant Correlations: $PM_{10-2.5}$: r = 0.2; PM_{10}: r = 0.67
†Lipsett et al. (2011) California, U.S. Prospective cohort $PM_{2.5}$: 1999–2005 Follow-up: 1995–2000	CTS N = 124,614 Avg follow-up: 5.6 yr	Multi-yr avg using IDW interpolation of monitors within 20 km (250 by 250 m grid) residential address	Mean:15.64 (SD: 4.48) IQR: 8.02 Range: 3.11–28.35	Incident MI (hospital records)	Copollutant model: NR Copollutant Correlations: PM_{10}: r = 0.91, NO_2: r = 0.81, CO: r = 0.53, SO_2: r = 0.02
†Puett et al. (2011) NE and MW, U.S. (13 contiguous states) Prospective cohort $PM_{2.5}$: 1988–2002 Follow-up: 1989–Jan 2003	HPFU n = 51,529 males	Annual avg at residential address, spatiotemporal model with monthly surface $PM_{2.5}$ measurements; (C-V R^2 = 0.77, and 0.69; precision = 2.2 and 2.7 µg/m^3, (post-1999 and pre-1999, respectively) see Yanosky et al. (2009) for details	Mean: 17.8 (SD: 3.4) IQR: 4.3	Nonfatal MI (medical record review)	Copollutant model: $PM_{10-2.5}$ Copollutant correlations: NR

Table 6-35 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and ischemic heart disease.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Madrigano et al. (2013) Worcester, MA Incident case control Exposure: 2000 Cases: 1995–2003	Worcester Heart Attack Study n = 4,467 Acute MI cases; n = 9,072 controls	Annual avg at residential address, spatiotemporal model with monthly surface $PM_{2.5}$ measurements; Observations of AOD calibrated to LUR (78 monitors); exposure (10 by 10 km grid) Mean out-of-sample R^2 = 0.85 (Kloog et al., 2011)	Mean (area $PM_{2.5}$): 9.43 (SD: 44); Mean (local $PM_{2.5}$) 1.07 (SD: 1.56); Mean (total $PM_{2.5}$): 10.5 (SD: 1.55)	Confirmed AMI	Copollutant model: regional $PM_{2.5}$ adjusted for local $PM_{2.5}$ from traffic Copollutant correlations: NR
†Hartiala et al. (2016) Ohio, U.S. Prospective $PM_{2.5}$: 1998–2010 Outcome 2001/07–2010	N = 6,575 Ohio residents undergoing elective cardiac evaluation	3-yr avg IDW interpolation at zip code centroid	Mean: 15.5 SD 1.1	Confirmed MI (adjudicated diagnosis)	NO_2 r = 0.15 Copollutant model: NR
†Cesaroni et al. (2014) 11 Cohorts in Finland, Sweden, Italy, Denmark and Germany Prospective cohort $PM_{2.5}$: 2008–2011 Follow-up: 1992–2007, depending on cohort	ESCAPE N = 100,166 Avg follow-up: 11.5 yr	Annual avg $PM_{2.5}$ estimated by LUR with input from measurements from 20 locations per study area Model performance R^2 ≥0.61	Mean ranged from 7.3 (SD = 1.3) to 31 (1.7)	IHD (hospital records)	Copollutant models: NR Correlations available for each cohort reported
†Hoffmann et al. (2015) Prospective cohort $PM_{2.5}$: Aug 2008–Sep 2009 Outcome: 2000/03 (baseline)	HNR study N = 4,433 Avg follow-up: 7.9 yr	Annual avg $PM_{2.5}$ at residential address estimated by LUR with input from 20 locations	Mean: 18.4	MI, sudden cardiac death and fatal CHD Medical record review by committee	Copollutant models: NR Copollutant correlations: NR
†Atkinson et al. (2013) 205 medical practices, U.K. Prospective cohort $PM_{2.5}$: 2002 Follow-up:2003–2007	General Practice database N = 836,557 patients (40–89 yr)	Annual avg (2002) estimated using dispersion model (1 by 1 km grid) linked to residential postal code $PM_{2.5}$ model validation: R^2 = 0.5 (correlation with national air quality network)	Mean 12.9 (SD 1.4) Range 7.2–20.2 IQR: 1.9	MI (medical records)	Copollutant models: NR PM10 r = 0.99, SO_2 r = 0.53; NO_2 r = 0.87; O_3 r = −0.43

Table 6-35 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and ischemic heart disease.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Tonne et al. (2015) Greater, London Prospective cohort $PM_{2.5}$: 2003–2010 Follow-up: 2003/07–2010	MINAP (MI Survivors) N = 18,138 Avg follow-up 4 yr	Annual avg estimated using dispersion models (20 by 20 m grid) time-varying exposure assigned within 100 m of patients' residential postal code centroid	Mean: 14.6 (SD: 1.3); IQR: 1.5	Readmission for STEMI or non-STEMI and death combined	Copollutant models: NR Copollutant correlations: PM_{10} r = 0.96; O_3 r = −0.82, NO_X r = 0.73; NO_2 r = 0.71
†Koton et al. (2013) 8 Medical Centers, Israel $PM_{2.5}$: 2003–2005 Follow-up: 1992/93–2005	Post-MI patients (≥65 yrs) admitted to medical centers Avg follow-up 13.2 yr N = 341	Multi-yr avg at residence, kriging interpolation (12 monitors); Imputed values uncertainty lower than 7 µg/m³ (C-V error 1.6–6% overall)	Median: 23.9 (Range: 17.0–26.6)	Recurrent MI, heart failure, stroke or TIA	Copollutant models: NR Copollutant correlations: NR

AOD = Aerosol optical depth, Avg = average, CHD = coronary heart disease, C-V = cross-validation, CTS = California Teacher Study, ESCAPE = European Study of Cohorts for Air Pollution, HPFU = Health Professionals Follow-up, IQR = interquartile range, LUR = land use regression, MINAP = Myocardial Ischemia National Audit Project; MI = myocardial infarction, N, n = number of subjects, NHS = Nurses' Health Study, NR = not reported; STEMI = ST elevation myocardial infarction; TIA = transient ischemic attack; WHI = Women's Health Initiative, Yr = years

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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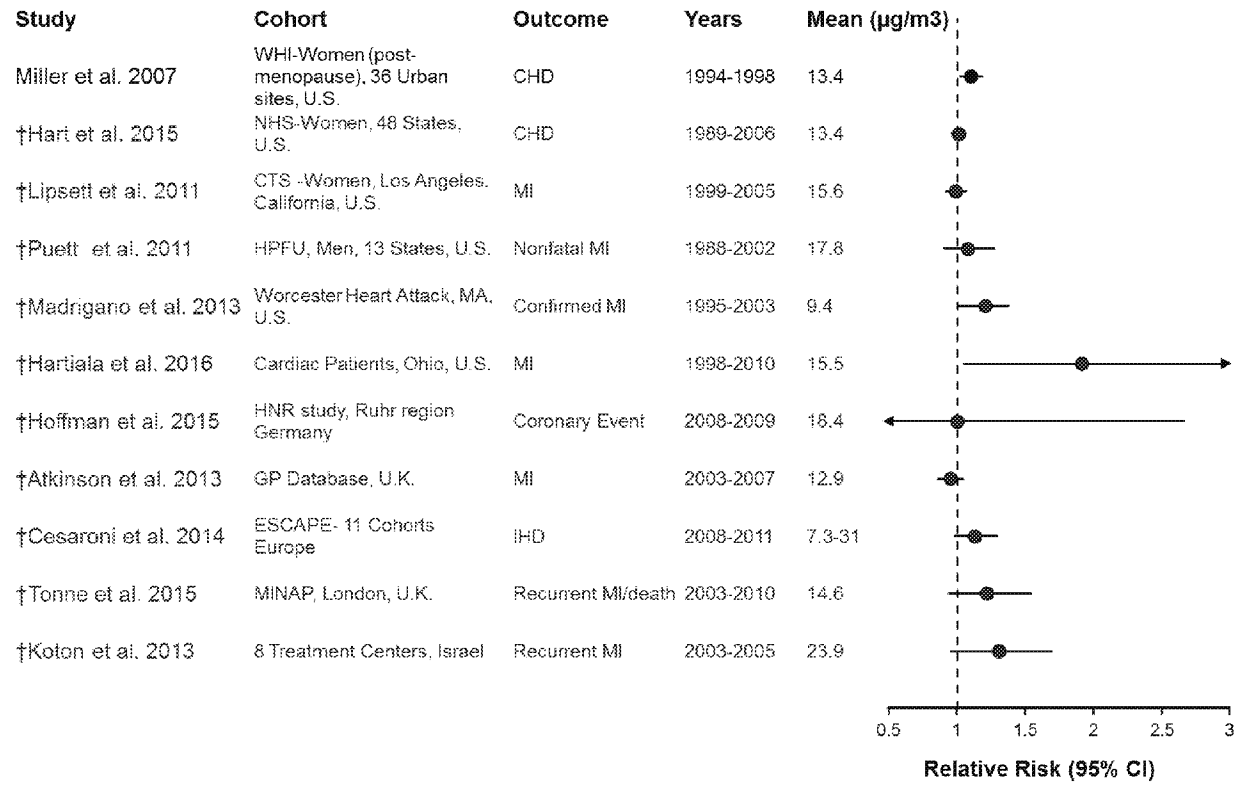
Associations in prospective cohort studies are presented in Figure 6-17. In a large, prospective study reviewed in the 2009 PM ISA, Miller et al. (2007) reported a hazard ratio (HR) for incident CHD morbidity and mortality of 1.10 (95%CI: 1.02, 1.19) among post-menopausal women. Several recent studies have followed up on this finding by examining the effect of long-term exposure to $PM_{2.5}$ in women. Hart et al. (2015b) observed no association between long-term exposure to $PM_{2.5}$ and incident CHD among women enrolled in the Nurses' Health Study (NHS) [HR: 1.01 95%CI: 0.96,1.07] although increased CHD risk was observed among women with diabetes [HR: 1.10 95%CI: 0.99,1.21]. The women in NHS were younger (38% premenopausal) than the women in the WHI, potentially explaining the discrepancy in the findings between these studies. In an analysis of women enrolled in the California Teachers' Study (CTS), Lipsett et al. (2011) reported no association with incident MI (hospitalizations and deaths combined) [HR: 0.99 (95%CI: 0.91, 1.08)], although increased risks of fatal IHD (see Section 6.2.10) and stroke were observed (see Section 6.2.3). Results from a CTS sensitivity analysis that was restricted to post-menopausal women did not indicate a positive association (Lipsett et al., 2011).

The remaining North American studies, which examined populations of men, or both men and women, generally report positive associations between long-term $PM_{2.5}$ exposure and MI, although the width of the confidence intervals varies between studies. Puett et al. (2011) conducted a prospective analysis of the Health Professionals Follow-up Study (HPFS), which consists of male medical professionals reporting an association of 1.08 (95%CI: 0.90, 1.28). This association was largely unchanged after adjustment for $PM_{10-2.5}$ (Puett et al., 2011). In an incident case control analysis of confirmed acute MI Madrigano et al. (2013) reported a stronger association [OR: 1.21 (95%CI: 1.00, 1.38)] between long-term exposure to $PM_{2.5}$ and acute MI. This study derived exposure metrics to distinguish regional $PM_{2.5}$ from local traffic-related $PM_{2.5}$ sources of exposure, and found the association with regional $PM_{2.5}$ was not attenuated in a copollutant model containing local traffic-related $PM_{2.5}$. A limitation of this study was its lack of adjustment for smoking. In another study, Hartiala et al. (2016) reported an association of long-term exposure to $PM_{2.5}$ with confirmed MI among those undergoing cardiac evaluation at a clinic in Ohio. Notably, Madrigano et al. (2013) and Hartiala et al. (2016) confirmed potential cases of MI.



†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in µg/m^3. Hazard Ratios are standardized to a 5 µg/m^3 increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table 6S-16 (U.S. EPA, 2018). WHI = Women's Health Initiative; CHD = Coronary Heart Disease; MI = Myocardial Infarction; IHD = Ischemic Heart Disease; NHS = Nurses Health Study; CTS = California Teachers Study; HPFU = Health Professionals Follow-up Study; ESCAPE = European Study of Cohorts for Air Pollution; HNR = Heinz Nixdorf Recall study; MINAP = Myocardial Ischemia National Audit Project.

Figure 6-17 Associations between long-term exposure to $PM_{2.5}$ and Ischemic Heart Disease or Myocardial Infarction. Associations are presented per 5 µg/m^3 increase in pollutant concentration.

Several European studies examined the association of long-term $PM_{2.5}$ and IHD or MI reporting somewhat inconsistent across cohorts. A study from the European ESCAPE project, which includes 11 cohorts in five European countries (Finland, Sweden, Denmark, Germany, and Italy) (Cesaroni et al., 2014) is available for review. Average annual exposure to $PM_{2.5}$ was assigned using the area-specific land use regression models. Cohort specific hazard ratios were variable and the meta-analytically combined effect estimate for $PM_{2.5}$ was [HR: 1.13 (95%CI: 0.98, 1.30)]. In sensitivity analyses the authors considered exposures below various thresholds of average $PM_{2.5}$ concentrations. For the seven cohorts with participants exposed to <15 µg/m^3 average annual $PM_{2.5}$, the meta-analyzed hazard ratio was 1.19 (1.00, 1.42). The outcome determination in the ESCAPE project was cohort-specific, but most cohorts

used ICD codes linked with hospital and death records and defined incidence based on outcome dates. Although most of the cohorts did not include physician review and adjudication for case identification, a separate analysis of data from the HNR study (Hoffmann et al., 2015), with case review by an independent committee, reported no association between coronary events (MI, fatal CHD and sudden death) and long-term $PM_{2.5}$ exposures, after adjustment for noise and other covariates [HR: 1.00 (95%CI: 0.38, 2.67)], although an association with stroke was observed (Section 6.2.3). The confidence intervals from the HNR study were wide due to the small number of cases (n = 135 for coronary events). In another European study, Atkinson et al. (2013) reported a negative association between long-term $PM_{2.5}$ exposure and MI ascertained from a database of information from general practitioners in the U.K. Studies of recurrent MI among MI survivors yielded positive associations (Tonne et al., 2015; Koton et al., 2013). Koton et al. (2013) treated several important confounders (e.g., smoking) as time-varying and both Koton et al. (2013).

Several cross-sectional analyses, including analyses of U.S. national survey data, are available to consider the association of long-term $PM_{2.5}$ exposure with prevalent IHD or hospital admissions (To et al., 2015; Beckerman et al., 2012; Feng and Yang, 2012; Gan et al., 2011). Overall, results from these studies do not provide consistent evidence of an association and only Gan et al. (2011) considered the temporality of the association.

In summary, some well-conducted prospective studies indicate an association between long-term exposure to $PM_{2.5}$ and IHD outcomes in post-menopausal women (Miller et al., 2007) and in a meta-analysis of European cohorts (Cesaroni et al., 2014). Studies also indicate the potential for those with pre-existing disease to be at elevated risk of IHD morbidity [e.g., diabetics in the NHS (Hart et al., 2015b), cardiac patients (Hartiala et al., 2016) or those who experienced a previous MI (Tonne et al., 2015; Koton et al., 2013)]. Most studies considered important covariates such as menopausal status, hormone replacement therapy, smoking and SES. Although the WHI analysis of Miller et al. (2007) did not adjust for SES, Chi et al. (2016a) considered both individual and neighborhood level SES in a subsequent WHI analysis of combined coronary events (see Section 6.2.9), reporting that the association remained unchanged after adjustment for these factors. Lipsett et al. (2011) reported no association between $PM_{2.5}$ exposure and incidence of MI in the CTS, including in a sensitivity restricted to post-menopausal women; however, it is notable that an association with cardiovascular-related mortality was observed in this study. Similarly, no association with coronary events was observed in the HNR study but an association with stroke was reported (Hoffmann et al., 2015). The risk estimate reported by Miller et al. (2007) was for coronary events (i.e., morbidity and mortality combined) providing coherence for the evidence of consistent positive associations between long-term $PM_{2.5}$ exposure and mortality from cardiovascular causes. Several exposure assessment methods including spatiotemporal models and LUR were applied but not studies examined the influence of the choice of exposure model within a study. Consideration of confounding by copollutants was limited while correlations reported between pollutants varied by cohort but were generally moderate to high (Table 6-35).

6.2.3 Cerebrovascular Disease and Stroke

Cerebrovascular disease typically includes conditions hemorrhagic stroke, cerebral infarction (i.e., ischemic stroke) and occlusion of the precerebral and cerebral arteries (see Section 6.1.5). The 2009 PM ISA identified one study that indicated a positive association between $PM_{2.5}$ and cerebrovascular morbidity and mortality in post-menopausal women (Miller et al., 2007). Although the results are not entirely consistent across studies or stroke subtype, some recent well-conducted studies also support a positive association between long term exposure to $PM_{2.5}$ and stroke.

6.2.3.1 Epidemiologic Studies

Studies of the association between long-term exposure to $PM_{2.5}$ and cerebrovascular diseases are summarized in Table 6-36.

Table 6-36 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cerebrovascular disease.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
Miller et al. (2007) 36 metro areas, U.S. Prospective cohort $PM_{2.5}$: 2000 Follow-up: 1994–1998	WHI observational cohort N = 65,893 Median follow-up: 6 yr	Annual avg of closest monitor (2000), most women within 10 km of monitor	Median 13.4 IQR 11.6–18.3	CBVD Stroke Medical record review by physician adjudicators	Copollutant model: NR Copollutant correlations (*r*): NR
†Hart et al. (2015b) U.S. (contiguous states) Prospective cohort $PM_{2.5}$: 1989–2006 Follow-up: 1988–2006	NHS N = 114,537 Follow-up: ~16 yr	Annual avg at residential address, spatiotemporal model with monthly surface $PM_{2.5}$ measurements; (C-V R^2 0.76 and 0.77 pre- (limited $PM_{2.5}$ data) and post-1999, respectively) See Yanosky et al. (2009)	Mean (1989–2006): 13.4 (SD:3.3) Mean: 2000–2006: 12 (SD: 2.8)	Self-reported physician diagnosed Stroke	Copollutant model: NR Copollutant correlations (*r*): $PM_{10-2.5}$: *r* = 0.2; PM_{10}: *r* = 0.67
†Lipsett et al. (2011) California, U.S. Prospective cohort $PM_{2.5}$: 1999–2005 Follow-up: 1995–2000	CTS N = 124,614 Avg follow-up: 5.6 yr	Multi-year avg using IDW interpolation of monitors within 20 km (250 by 250 m grid) residential address	Mean:15.64 (SD: 4.48) IQR: 8.02 Range: 3.11–28.35	Incident Stroke (hospital records)	Copollutant model: NR Copollutant correlations(*r*): PM_{10}: *r* = 0.91, NO_2: *r* = 0.81, CO: *r* = 0.53, SO_2: *r* = 0.02
†Puett et al. (2011) Northeast and Midwest, US (13 contiguous states) Prospective cohort $PM_{10-2.5}$: 1988–2002 Follow-up: 1989–Jan 2003	Health Professionals Follow-up Study N = 51,529 Avg follow-up NR	Annual avg at residential address, spatiotemporal model with monthly surface $PM^{2.5}$ measurements; C-V R^2 = 0.77, and 0.69; precision = 2.2 and 2.7 µg/m^3, (post-1999 and pre-1999, respectively) see Yanosky et al. (2009)	Mean: 17.8 (SD: 3.4) IQR: 4.3	IS, HS (medical record review)	Copollutant model: $PM_{10-2.5}$ Copollutant correlations(*r*): NR

Table 6-36 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cerebrovascular disease.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Hartiala et al. (2016) Ohio, U.S. $PM_{2.5}$: 1998–2010 Outcome 2001/07–2010	N = 6,575 Cardiac evaluation patients Ohio residents	3-yr avg IDW interpolation at zip code centroid	Mean: 15.5 SD 1.1	stroke	Copollutant correlations(*r*): NO_2 = 0.15 Copollutant model: NR
†Stafoggia et al. (2014) 11 Cohorts in Finland, Sweden, Italy, Denmark and Germany Prospective cohort $PM_{2.5}$: 2008–2011 Follow-up: 1992–2007, depending on cohort	ESCAPE 99,446	Annual avg $PM_{2.5}$ estimated by LUR with input from measurements from 20 locations per study area Model performance: R^2 ≥0.61	Mean ranged from 7.3 (SD = 1.3) to 31 (1.7)	CBVD (medical and death record review)	Copollutant model: NR Copollutant correlations (*r*): NR
†Hoffmann et al. (2015) Ruhr region, Germany Follow-up: 2000/03–2012 $PM_{2.5}$: Aug 2008–Jul 2009	HNR study N = 4,433	Annual avg $PM_{2.5}$ estimated by LUR with input from measurements from 20 locations per study area Model performance: R^2 ≥0.61 see Cesaroni et al. (2014)	Mean 18.4 (SD 1.06); 5–95th: 3.51	Self-reported stroke with medical record review	Copollutant model: NR Copollutant correlations (*r*): NR
†Atkinson et al. (2013) U.K. Prospective cohort $PM_{2.5}$: 2002 Follow-up:2003–2007	General Practice database N = 205 practices N = 836,557 patients (40–89 yrs)	Annual avg (2002), dispersion model (1 by 1 km grid) at residential postal code $PM_{2.5}$ model validation: R^2 = 0.5 (correlation with national air quality network)	Mean 12.9 (SD 1.4) Range 7.2–20.2 IQR: 1.9	Stroke (medical records ICD10 I61)	Copollutant model: NR Copollutant correlations (*r*): PM_{10} *r* = 0.99, SO_2 *r* = 0.53; NO_2 *r* = 0.87; O_3 *r* = −0.43

Table 6-36 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cerebrovascular disease.

Study	Study Population	Exposure Assessment	Concentration $\mu g/m^3$	Outcome	Copollutants Examined
†Koton et al. (2013) 8 Medical Centers, Israel $PM_{2.5}$: 2003–2005 Follow-up: 1992/93–2005	Post-MI patients (≥65 yrs) admitted to medical centers Avg follow-up 13.2 yrs N = 160 cases	Multi-yr avg at geocoded residential address, kriging interpolation (12 monitors) Imputed values with kriging uncertainty lower than 7 $\mu g/m^3$ (C-V error 1.6–6% overall)	Median: 23.9 (Range: 17.0–26.6)	Recurrent stroke or TIA	Copollutant model: NR Copollutant correlations (*r*): NR

Avg = average, AOD = Aerosol optical depth, CBVD = cerebrovascular disease, CTS = California Teacher Study, C-V = cross-validation, ESCAPE = European Study of Cohorts for Air Pollution; FSA Forward Sortation Area; HS = Hemorrhagic Stroke; HNR = Heinz Nixdorf Recall study; ICD = International Classification of Disease, IQR = interquartile range, IS = Ischemic Stroke, MINAP = Myocardial Ischemia National Audit Project, NHS = Nurses' Health Study, N (n) = number of subjects, NR = not reported, SD = standard deviation, TIA = transient ischemic attack, yrs = years

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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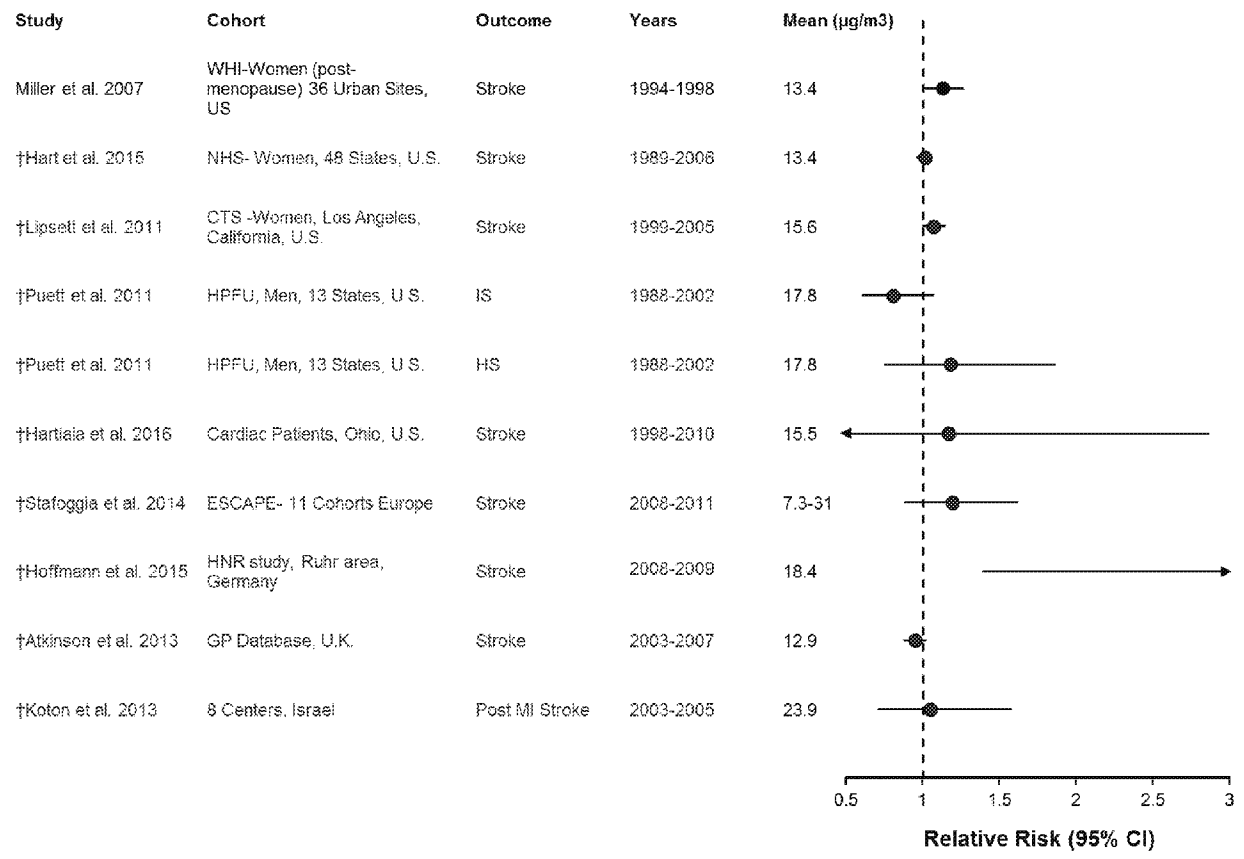
Prospective studies of the association between long-term $PM_{2.5}$ exposure and the incidence of stroke are presented in Figure 6-18. In a study reviewed in the 2009 PM ISA Miller et al. (2007) reported associations of both CBVD and stroke with long-term exposure to $PM_{2.5}$ among post-menopausal women enrolled in WHI who were free of the conditions at baseline [HR: CBVD: 1.16 (95%CI: 1.04, 1.30) and HR stroke: 1.13 (95%CI: 1.04, 1.30)]. Several recent studies conducted in cohorts of women are available for comparison to the WHI findings. The CTS reported associations of $PM_{2.5}$ on incident stroke [HR: 1.07 (95%CI: 0.99, 1.15)] (Lipsett et al., 2011). The association with incident stroke did not include the null value when the sample was restricted to postmenopausal women [HR: 1.09 (95%CI: 1.01, 1.17)]. A prospective analysis of the relatively younger women enrolled in the NHS, reported an increased risk among women with diabetes [HR: 1.29 (95%CI: 1.14, 1.45)] but not in the population, overall [HR: 1.01 (95%CI: 0.96, 1.05)] (Hart et al., 2015b).

Several U.S. studies of men or men and women combined were also available for review. In a cohort of men enrolled in the HPFU study, Puett et al. (2011) examined the effect of long-term exposure to $PM_{2.5}$ on hemorrhagic stroke (HS) and ischemic stroke (IS), classified using National Survey of Stroke criteria and reviewed by physicians. The number of case was small (n = 230 for IS and n = 70 for HS), resulting in estimates with wide CIs [HR: 0.80 (95%CI: 0.61, 1.08)] for IS and HR: 1.18 (95%CI: 0.74, 1.85) HS]. In a study of cardiac patients in Ohio, Hartiala et al. (2016) reported an imprecise association (i.e., wide confidence intervals) between long-term exposure to $PM_{2.5}$ and stroke [HR: 1.17 (95%CI: 0.49, 2.87)] that was attenuated in fully adjusted models that considered a large array of cardiovascular risk factors (i.e., obesity smoking, physical activity and land use development).



†Studies published since the 2009 Integrated Science Assessment for Particulate Matter. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Mean concentrations in $\mu g/m^3$. Hazard Ratios are standardized to a 5- $\mu g/m^3$ increase in $PM_{2.5}$ concentrations. Corresponding quantitative results are reported in Supplemental Table 6S-17 (U.S. EPA, 2018). MI = Myocardial Infarction; IS = ischemic stroke; HS = hemorrhagic stroke; WHI = Women's Health Initiative; NHS = Nurses' Health Study; HPFU = Health Professional's Follow-up; ESCAPE = European Study of Cohorts for Air Pollution; HNR = Heinz Nixdorf Recall; GP = General Practitioner.

Figure 6-18 Associations between long-term exposure to $PM_{2.5}$ and the incidence of stroke. Associations are presented per 5 $\mu g/m^3$ increase in pollutant concentration.

Within the European ESCAPE study, long-term exposure to $PM_{2.5}$ was positively associated with incident stroke [HR: 1.19 (95%CI: 0.88, 1.62)] in the fully adjusted model, which included variables to control for SES (Stafoggia et al., 2014). Researchers observed a more precise result when restricting to the six cohorts for which the LUR model performed the best (R^2>0.6) [HR 1.75 (1.30, 2.35)]. Additionally, stratified analyses indicated that effects may be larger in magnitude in older age groups and among never-smokers. The authors restricted the analysis to individuals exposed to <15 $\mu g/m^3$ concentrations of $PM_{2.5}$ and observed a HR of 1.33 (95%CI: 1.01, 1.77). As mentioned previously, most ESCAPE cohorts did not have physician review and adjudication of cases. A separate analysis of data

from the HNR study, one of the ESCAPE cohorts, with case review by an independent committee, reported a relatively large association between long-term $PM_{2.5}$ exposure and stroke that persisted after adjustment for noise [HR: 5.24 (95%CI: 1.39, 19.65).] In contrast to these studies indicating an association between $PM_{2.5}$ and stroke, the previously described English general practice database found no association; however, cases were not validated by physician review and the $PM_{2.5}$ prediction model performance was relatively low ($R^2 = 0.5$) (Atkinson et al., 2013). A final study examined the effect of $PM_{2.5}$ on first stroke and recurrent stroke in a cohort of Israeli first MI patients (Koton et al., 2013). Numbers of events were small and exposures higher than some areas in the US (median $PM_{2.5}$: 23.9 $\mu g/m^3$); however, cases were validated by physician review and analyses included time-varying confounders. The study reported an imprecise relationship between $PM_{2.5}$ and the first stroke after MI [HR: 1.05 (95%CI: 0.71, 1.58)] but a larger magnitude association for recurrent strokes [HR: 1.22 (95%CI: 0.95, 1.55)].

Several cross sectional or ecological analyses of prevalent stroke or first hospital admission for stroke that provide some support for the associations observed in prospective studies were also conducted (To et al., 2015; Feng and Yang, 2012; Johnson et al., 2010).

In summary, studies of women enrolled in the WHI study and in the CTS support a positive association between long term exposure to $PM_{2.5}$ and stroke (Lipsett et al., 2011; Miller et al., 2007). Hart et al. (2015b) reported an association in women with diabetes but not in the NHS population, overall. Evidence was inconsistent across other populations studied and confidence intervals around effect estimates were generally wide (Figure 6-18). Several studies are limited by lack of physician adjudication of stroke and outcomes and small sample sizes for stroke subtype analyses. The exposure assessment methods that were applied varied by study but included spatiotemporal models and LUR. There was no evaluation of the influence of the exposure model choice within a study and analysis of copollutant confounding was limited.

6.2.3.1.1 Subclinical Cerebrovascular Disease

Various diagnostic tools can be used to examine risk of cerebrovascular disease. Cerebrovascular hemodynamics, measured through transcranial Doppler ultrasound, is an important component of assessing cerebrovascular blood flow. White matter hyperintensity, detected through magnetic resonance imaging (MRI), is thought to be caused in part by ischemia in the brain and has been shown to predict stroke, dementia, and death (Debette and Markus, 2010). Covert or silent brain infarcts can also be detected with MRI. Both white matter hyperintensity and covert brain infarcts can appear in persons with no history of clinical cerebrovascular event history, and can therefore be used as markers of subclinical disease in asymptomatic individuals. Recent epidemiologic studies have examined subclinical measures of cerebrovascular disease. No studies of this type were available for the 2009 PM ISA (U.S. EPA, 2009). There is a paucity of laboratory animal studies on stroke and cerebrovascular disease with long-term particle exposure. There were no studies on this endpoint in the 2009 PM ISA, and no new studies have

been published since. The nervous system chapter in this ISA reviews studies of brain morphology that are relevant to cerebrovascular disease.

Wellenius et al. (2013) assessed cerebrovascular hemodynamics within the NAS, a cohort of older adults in Boston, by calculating cerebrovascular resistance (i.e., mean arterial blood pressure/middle cerebral artery blood flow velocity) at rest as well as in response to a CO_2 challenge (i.e., induces cerebral vasodilation and increased blood flow) and a sit-to-stand maneuver (i.e., cerebral autoregulation). While no effects of $PM_{2.5}$ were observed on cerebral vasoreactivity or autoregulation, there was an effect of 28-day average $PM_{2.5}$ on increasing resting cerebrovascular resistance [14.33% (95%CI: 6.17, 23.00) due to a decreasing resting middle cerebral artery blood flow [-12.50% (95%CI: -17, 7.0,) (Wellenius et al., 2013). Wilker et al. (2015) examined the effect of $PM_{2.5}$ on white matter hyperintensity and presence of covert brain infarcts (binary) among participants with no history of dementia, stroke, or transient ischemic attack. While there was little evidence of a $PM_{2.5}$ association with white matter hyperintensity, a predictor of stroke, there was a relationship with the presence of cerebral brain infarcts [OR: 2.20 (95%CI: 1.05, 4.66)]. Although studies are limited in number, they provide some evidence to support an effect of $PM_{2.5}$ on cerebrovascular conditions in participants exposed to average $PM_{2.5}$ exposures 12.6-12.1 $\mu g/m^3$ [(Wellenius et al., 2013) and (Wilker et al., 2015), respectively].

6.2.4 Atherosclerosis

Atherosclerosis is the process of plaque buildup into lesions on the walls of the coronary arteries that can lead to narrowing of the vessel, reduced blood flow to the heart and IHD. The development of atherosclerosis is dependent on the interplay between plasma lipoproteins, inflammation, endothelial activation, and neutrophil attraction to the endothelium, extravasation, and lipid uptake. Risk factors for atherosclerosis include high LDL/low HDL cholesterol, high blood pressure, diabetes, obesity, smoking and increasing age. The 2009 PM ISA reviewed a series of cross-sectional studies examining measures that assessed atherosclerosis within large arterial vascular beds in distinct regions of the body [i.e., carotid intima-media thickness (CIMT), coronary artery calcium (CAC), and ankle-brachial index (ABI).] Overall, findings from these studies were inconsistent, with studies reporting null or positive imprecise associations with CIMT, CAC, and ABI (U.S. EPA, 2009). Exposure measurement error, variation in baseline measures of atherosclerosis as well as statistical power were noted as possible explanations for the lack of association observed in these studies. Although findings from more recent studies are not entirely consistent across populations and measures of atherosclerosis, an extended MESA analysis reported a longitudinal increase in coronary artery calcification (CAC) (Kaufman et al., 2016) At the time the 2009 ISA was completed, the biological plausibility for $PM_{2.5}$ induced atherosclerotic plaque development was provided by a small number of experimental animal studies, with several of the experiments conducted in the same laboratory (U.S. EPA, 2009). An additional experimental study is currently available for review.

6.2.4.1 Epidemiologic Studies

Studies that examine the relationship between long-term exposure to $PM_{2.5}$ and measures of atherosclerosis are characterized in Table 6-37.

Table 6-37 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and atherosclerosis.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Kaufman et al. (2016) 6 urban sites, U.S. Prospective cohort $PM_{2.5}$: 2005-2009 Follow-up:2000-2010/12	MESA 45-84 yrs (baseline) N = 3,459 Follow-up: 10 yrs	Annual avg derived from individual-weighted indoor and outdoor ambient $PM_{2.5}$ spatio-temporal model with residential history, Model fit R^2 = 0.90-0.97 C-V R^2 = 0.72 (0.54-0.85 depending on site)	Mean: 14.2 (range: 9.2-22.6) IQR range: 12.9-15.7	cIMT CAC	Copollutant model: NR Copollutant correlations (*r*): NR
†Chi et al. (2016b) 4 urban sites, U.S Cross-sectional Follow-up:2000-2010/12	MESA N = 1,207 ≥55 yrs	Annual avg prior to blood draw, at residence using spatiotemporal model see (Keller et al., 2015)	10.7 IQR: 2.2	DNA methylation in circulating monocytes	Copollutant model: NR Copollutant correlations (*r*): NR
†Dorans et al. (2016) $PM_{2.5}$: 2003-2009 Outcome: 2002-2005 and 2008-2011	Framingham Heart Study Offspring N = 3,399	Annual avg at grid of residence (1 x 1 km), spatiotemporal model, C-V R^2 = 0.88)	Median (IQR) = 10.7 (1.4) for 2003 Median (IQR) = 9.8 (1.1) for 2003-2009	CAC	Copollutant model: NR Copollutant correlations (*r*): NR
†Hartiala et al. (2016) Ohio residents Prospective cohort $PM_{2.5}$: 1998-2010 Outcome: 2001-2007-2010	CAD patients N = 6,575 Follow-up = 3 yr	3-year avg using IDW interpolation at zip code level (within 50 km of monitor)	Mean = 15.5 (SD = 1.1)	Severity of atherosclerosis (vessels with ≥50% stenosis)	Copollutant model: NR Copollutant correlations (*r*): NR

Table 6-37 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and atherosclerosis.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Künzli et al. (2010) Los Angeles, CA Prospective analysis of 5 RCTs $PM_{2.5}$: 2000	Healthy Adults N = 1,483 40-82 yrs (baseline) VEAPS: 1996-2000 BVAIT: 2001-2006, EPAT: 1994-1998 TART: 1997-2000 WELLHART: 1995-2000 Avg follow-up: 2-3 yrs	Annual mean at residence, Kriging interpolation (25 x 25 m grid), 23 monitors Model performance: NR	Mean: 20.8 (SD2.4) IQR: 20.5-22.1	Change in cIMT	Copollutant model: Adjusted for proximity to traffic Copollutant correlations (*r*): NR
†Gan et al. (2014) Vancouver, Canada Prospective cohort $PM_{2.5}$: 2003 Follow-up: 2004/5 – 2009/11	M-CHAT N = 509 30-65 (baseline) Follow-up: ~5 yr	Annual mean at residence, LUR Model fit R^2 = 0.52; mean error-1.50 µg/m³	Mean 4.1 (SD: 1.45) IQR 1.4	Change in cIMT	Copollutant model: NR Copollutant Correlations: BC *r* = 0.13; NO_2 *r* = 0.45, NO *r* = 0.43; Noise *r* = 0.19
†Aguilera et al. (2016) 4 Cities, Switzerland Cross-sectional $PM_{2.5}$: 2001/02-2010/11 Outcome: 2010/2011	SAPALDIA 50 yrs (or older, baseline) N = 1,503	Multi yr avg at residential address (2001-2011) estimated using Gaussian dispersion models (200 by 200 m grid)	Mean 17 (SD: 2.0) (2001-2011) Annual avg: 15.2 (SD: 1.6)	cIMT	Copollutant model: NR Copollutant correlations (*r*): $PM_{2.5}$ last yr and 2001-2011 *r* = 0.96; $PM_{2.5}$ vehicular *r* = 0.80; $PM_{2.5}$ crustal 0.75; PNC 0.86, LDSA 0.94
Young Adults					
†Lenters et al. (2010) Utrecht, Netherlands Cross-sectional $PM_{2.5}$: 2000 Outcome: 1999-2000	ARYA N = 745	Annual avg (2000) at childhood home address using regional concentrations and LUR see (Beelen et al., 2008)	Mean 20.7 (SD: 1.2) 5th−90th: 16.5-19.9	cIMT (Pulse wave velocity discussed under arterial stiffness)	Copollutant model: NR Copollutant correlations (*r*): NO_2 *r*>0.5

Table 6-37 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and atherosclerosis.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†Breton et al. (2016) Retrospective cohort $PM_{2.5}$: 1980-2009 Outcome: 2007/2009	College Students TROY N = 768	Monthly avg to estimate prenatal exposure using IDW spatial interpolation at residential history (interpolation range 50 km unless data available within 5 km) Leave one out cross-validation: R^2 0.53	Mean 19.5 (SD: 6.1)	Carotid artery arterial stiffness and cIMT	Copollutant model: NR Copollutant correlations (*r*): 1st Trimester: O_3 *r* = -0.01, NO_2 *r* = 0.71, PM_{10} *r* = 0.89 (Note: generally consistent across trimesters)
†Breton et al. (2012) Retrospective cohort $PM_{2.5}$: 1980-2009 Outcome: 2007/2009	College Students TROY N = 768	Monthly avg to estimate childhood exposure (0-5 yrs, 6-12 yrs) and lifetime avg using IDW spatial interpolation at residential address (interpolation range 50 km unless data available within 5 km)	0-5 yrs: 18.2 (SD: 5.3) 6-12 yrs: 15.7 (SD 5.0) Lifetime: 15.7 (SD: 5.0)	cIMT	Copollutant model: NR Copollutant correlations (*r*): Age 0-5: NO_2 *r* = 0.77, O_3 *r* = 0.9, PM_{10} *r* = 0.89 Age 6-12: NO_2 *r* = 0.8, O_3 *r* = -0.15, PM_{10} *r* = 0.85 Lifetime: NO_2 *r* = 0.82, O_3 *r* = -0.04, PM_{10} *r* = 0.87

Avg = average, ARYA = Atherosclerosis Risk in Young Adults, BVAIT = B-Vitamin Atherosclerosis Intervention Trial, CTM = chemistry transport model, EPAT = Estrogen in the Prevention of Atherosclerosis Trial, IMPROVE = Stockholm, Sweden, KORA = Augsburg, Germany, LDSA = Lung deposited surface area, M-CHAT = Multicultural Community Health Assessment Trial, MESA = Multi-Ethnic Study of Atherosclerosis, RCTs = Randomized Controlled Trials, REGICOR = Girona area, Spain, SAPALDIA = Swiss cohort study on Air Pollution and Lung and Heart Diseases, TROY = Testing Responses on Youth, VEAPS = Vitamin E Atherosclerosis Progression Study, WELLHART = Women's Estrogen-Progestin Lipid-Lowering Regression Trial

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

1

Several analyses from the MESA Air cohort, which comprises a large ethnically diverse study population recruited between 2000 and 2002 from six U.S. communities thus allowing within-city contrasts. Recent analyses of this cohort contribute to the evidence describing the relationship between long-term exposure to $PM_{2.5}$ and atherosclerosis. In general, cross-sectional analyses that included control for study site reported no association regardless of $PM_{2.5}$ exposure assessment method (Adar et al., 2013; Sun et al., 2013). Results from an interim longitudinal analysis (Adar et al., 2013) showing a $PM_{2.5}$ associated increase in cIMT were not retained when additional years of follow-up were available (Kaufman et al., 2016). Kaufman et al. (2016) observed no association with cIMT [-0.9 mm (95%CI: -3.0, 5.0)] while reporting a 4.1 agatston unit increase per year (95%CI: 1.4, 6.8) for CAC. CAC is a stronger predictor of subsequent CHD than cIMT, which typically indicates earlier vascular injury than CAC, in MESA study participants (Gepner et al., 2015). The effect of $PM_{2.5}$ on CAC progression was stronger in people with hypertension, those who are not obese and older adults. Modification of this association by race was not observed. Also in the MESA cohort, Chi et al. (2016b) observed associations of long-term $PM_{2.5}$ exposure with DNA methylation in circulating monocytes. By contrast, Dorans et al. (2016) reported an imprecise (i.e., wide CIs) association between exposure to long-term $PM_{2.5}$ and CAC progression using defined thresholds based on the variability of within-person repeated CAC measurements in the Framingham Heart Study [OR: 1.23 (95%CI: 0.77, 1.92)]. The change in CAC in association with long-term exposure to $PM_{2.5}$ was also reported [-2.86 (95%CI: -8.57, 2.86)]. The shape of the concentration-response functions for these studies are discussed in Section 6.2.16.

Several other studies examined the longitudinal changes in atherosclerosis indicated by the presence of lesions or cIMT, but studies of CAC were not available for comparison to results reported in the MESA and Framingham Health Studies. Long-term exposure to $PM_{2.5}$ was associated with both mild and severe atherosclerosis, defined as ≥50 stenosis in 1-2 and >3 vessels, respectively among coronary artery disease patients in Ohio (Hartiala et al., 2016). Künzli et al. (2010) examined the relationship between long-term exposure to $PM_{2.5}$ and the rate of atherosclerosis progression reporting a small positive association of $PM_{2.5}$ with cIMT progression rate [1.27 μm/yr (95%CI: -0.16, 2.69)]. The association of $PM_{2.5}$ with cIMT in was more than twofold larger among those living within 100 meters of a highway, however. By contrast, Gan et al. (2014) observed no association with change in cIMT in a smaller sample (N = 509) in Vancouver Canada where the mean $PM_{2.5}$ concentration is relatively low (4 $\mu g/m^3$).

Several cross-sectional analyses examined atherosclerotic lesions and cIMT reported results that were not entirely consistent (Aguilera et al., 2016; Newman et al., 2015; Perez et al., 2015; Bauer et al., 2010). Studies of the effect of exposure during prenatal and childhood lifestages and atherosclerosis as young adults were also conducted. Among young adults in their twenties, neither Lenters et al. (2010) nor (Breton et al., 2012) observed large (relative the width of the confidence interval) increases in cIMT in association with $PM_{2.5}$ exposure, regardless of childhood exposure window [0.69 μm (95% CI: -4.41, 5.79) and -1.51 (95%CI: -5.19, 2.17)]. In an analysis focusing on prenatal exposure Breton et al. (2016) reported an imprecise (i.e., wide CIs) small magnitude association with $PM_{2.5}$ [1.48% increase in cIMT (95% CI: -1.77, 4.74)].

In summary, several epidemiologic studies have continued to examine the relationship between long-term $PM_{2.5}$ exposure and atherosclerosis among adults since the completion of the 2009 PM ISA. These studies were conducted within North America and Europe with some extending analyses of the same populations discussed in the 2009 PM ISA (i.e., MESA, HNR). A strength of the expanded body of literature is that it includes analyses of the longitudinal change in measures of atherosclerosis in relation to long-term exposure to $PM_{2.5}$ (Hartiala et al., 2016; Kaufman et al., 2016; Gan et al., 2014; Künzli et al., 2010). MESA analyses supported a $PM_{2.5}$ effect on CAC among middle to older aged adults, while the Dorans et al. (2016) analysis of Framingham Heart Study offspring did not provide support for an association with CAC progression or longitudinal change in CAC. Associations of long-term exposure to $PM_{2.5}$ with cIMT were not consistently observed across cohorts or when variable methods (e.g., exposure assessment methods) were applied within the same cohort. Relationships between $PM_{2.5}$ and CIMT at younger ages were generally not supported in the limited number of studies. Consideration of copollutant confounding was limited across the evidence base.

6.2.4.2 Toxicological Studies of Atherosclerosis

Atherosclerosis and related pathways have been studied primarily in the Apolipoprotein E (ApoE) knockout mouse (Piedrahita et al., 1992; Zhang et al., 1992), The ApoE molecule is involved in the clearance of fats and cholesterol. When ApoE (or the low- density lipoprotein (LDL) receptor) is deleted from the genome, mice develop severely elevated lipid and cholesterol profiles. As a result, the lipid uptake into the vasculature is increased and the atherosclerotic process is dramatically hastened. Furthermore, the LDLs in $ApoE^{-/-}$ mice are highly susceptible to oxidation (Hayek et al., 1994), These mice exhibit cholesterol levels exceeding 1,000 mgdL (normal is ~150 mgdL) (Moore et al., 2005; Huber et al., 1999). which may be a crucial event in the air pollution-mediated vascular changes. However, it should be noted that this model is primarily one of peripheral vascular disease rather than coronary artery disease.

In the 2009 PM ISA, studies found increased atherosclerotic plaque area in aortas of $ApoE^{-/-}$ mice exposed to $PM_{2.5}$ CAPs for 4-6 months from an exurban site located in Tuxedo NY or an urban site located in Manhattan, NY. Since the publication of the 2009 PM ISA, Lippmann et al. (2013a) have conducted additional plaque progression analyses in Irvine, CA; Lansing, MI; and Seattle, WA, as well as in Tuxedo and Manhattan, NY. The authors reported that plaque progression in $ApoE^{-/-}$ mice varied by site. Specifically, increased ($p < 0.05$) plaque areas relative to control animals were identified in the brachiocephalic artery of mice exposed to $PM_{2.5}$ from Manhattan, NY (6 mo after exposure), Tuxedo, NY (3 and 6 mo after exposure), and ($p < 0.05$) in East Lansing, MI. Increased (6 mo after exposure, $p < 0.05$) plaque progression relative to control animals was also identified in the left common carotid artery of mice exposed to $PM_{2.5}$ from Tuxedo (6 mo after exposure) and Irvine (2 mo after exposure). Animals exposed to $PM_{2.5}$ from Seattle did not have increased plaque progression relative to controls in either the brachiocephalic or the carotid arteries. However, it is important to note that the mice were older

in the studies performed in Seattle and Irvine. Therefore, the Seattle and Irvine mice were older at the onset of PM exposures than animals used in studies at the other sites and this could have affected the results of these studies. Nonetheless, the results in other locations provide evidence for $PM_{2.5}$-mediated effects on atherosclerotic plaque progression in a genetically susceptible mouse model. More information on this study can be found in Table 6-38 below.

Table 6-38 Study specific details from toxicological studies of long-term $PM_{2.5}$ exposure and atherosclerosis.

Study	Study Population	Exposure Details	Endpoints Examined
(Lippmann et al., 2013a) NPACT Study 1	$ApoE^{-/-}$ mice, M, n = 4–8 per treatment group	CAPs from Irvine, CA; Tuxedo, NY; Manhattan, NY, Lansing, MI; or Seattle, WA (138, 136, 123, 68, or 60 ug/m^3, respectively) for 6 h/day, 5 days/week for 6 mo	Atherosclerotic plaque progression by ultrasound 2 mo, 4 mo, and 6 mo post

$APOE^{-/-}$ = apolipoprotein E null mice, n = number d = day, h = hour, mo = month, CAPs = concentrated ambient particles, post = after exposure,

6.2.5 Heart Failure and Impaired Heart Function

Heart failure (HF) refers to a set of conditions including congestive heart failure (CHF) in which the heart's pumping action is weakened. With CHF the blood flow from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other tissues (typically in the legs and ankles). Risk factors for HF include IHD, high blood pressure, atrial fibrillation, and diabetes. Right sided HF, is typically a consequence of left-sided HF but can also result from damage to the pulmonary vasculature, which can result in increased right ventricular (RV) mass, reduced flow to the left ventricle and reduced left ventricular (LV) mass. In chronic HF, the heart typically enlarges and develops more muscle mass. LV mass is known to predict the development of HF and can be assessed with magnetic resonance imaging (MRI) (Drazner et al., 2004). Ejection fraction (EF), which is the percent of blood that is pumped from the ventricle during each contraction, is another measure of how well the heart pumps that can be assessed through echocardiography. Although depressed EF provides evidence of HF, EF may be normal in a large proportion of HF patients. There were no studies examining the association between long-term exposure to $PM_{2.5}$ and CHF reviewed in the 2009 PM ISA. The evidence has expanded substantially with the recent epidemiologic and toxicological studies providing support for an effect of long-term exposure to $PM_{2.5}$ on CHF and impaired cardiac function.

6.2.5.1 Epidemiologic Studies

There were no epidemiologic studies examining the association between long-term exposure to $PM_{2.5}$ and CHF reviewed in the 2009 PM ISA (U.S. EPA, 2009). A small number of recent studies have examined the effects of $PM_{2.5}$ on heart failure or related indices (Table 6-39) generally reporting positive associations. The U.K. general practice cohort described in Section 6.2.2, which included nearly 13,000 cases of incident heart failure identified by ICD codes with physician review, reported a positive association with long-term exposure to $PM_{2.5}$ [HR 1.17 (95%CI: 1.03, 1.17)] (Atkinson et al., 2013). A relatively small Israeli cohort was exposed to higher $PM_{2.5}$ concentrations than most areas of the U.S. (median [range]: 23.9 [17.0-26.6]), and benefitted from physician review of medical records for case ascertainment and reported a HR for heart failure and recurrent heart failure after first MI with increasing $PM_{2.5}$ of 1.22 (95%CI: 0.89, 1.67) (Koton et al., 2013). A cross-sectional analysis of women reported a positive association between $PM_{2.5}$ and the prevalence of heart failure [OR: 1.14 (95%CI: 1.06, 1.23)] (To et al., 2015).

Table 6-39 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and heart failure.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†(Atkinson et al., 2013) U.K. Prospective cohort $PM_{2.5}$: 2002 Follow-up:2003-2007	General Practice database N = 205 practices N = 836,557 patients (40-89)	Annual avg (2002) dispersion model (1 by 1 km grid) at residential postal code $PM_{2.5}$ model validation: R^2 = 0.5 (correlation with national air quality network)	Mean 12.9 (SD 1.4) Range 7.2-20.2 IQR: 1.9	Heart Failure ICD10 I50)	Copollutant model: NR Copollutant correlations (*r*): PM_{10} *r* = 0.99, SO_2 *r* = 0.53; NO_2 *r* = 0.87; O_3 *r* = -0.43
†Koton et al. (2013) 8 Medical Centers, Israel $PM_{2.5}$: 2003-2005 Follow-up: 1992/93 – 2005	Post-MI patients (≥65 yrs) admitted to medical centers Avg follow-up 13.2 yrs N = 258	Multi-yr avg estimated using kriging interpolation (12 monitors); exposure assigned based on geocoded residential address Imputed values with kriging uncertainty lower than 7 µg/m³ (cross-validation error 1.6-6% overall)	Median: 23.9 (Range: 17.0-26.6)	Heart failure re-admission	Copollutant model: NR Copollutant correlations (*r*): NR
†(Van Hee et al., 2009) 6 Communities, U.S. Cross-sectional $PM_{2.5}$: 2000 Baseline exam: 2000-02	MESA N = 6,814	Annual avg kriging interpolation at residential address	Range of annual mean ~ 12-22	LVMI (cardiac MRI)	Copollutant model: NR Copollutant correlations (*r*): NR

Table 6-39 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and heart failure.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome	Copollutants Examined
†(Aaron et al., 2016) $PM_{2.5}$ 1999-2001 MRI: 2000-2002	MESA N = 4,204 45-84 yrs	Spatiotemporal Model to estimate annual average concentration at residence. Secondary model to estimate individually weighted $PM_{2.5}$ concentration using infiltration fraction	Mean: 16.4 SD: 3.4 (ambient) Mean 11 SD: 3.7	RV mass, volume, EF	Copollutant model with $PM_{10-2.5}$, NO_2 (D'Souza et al., 2017) Copollutant correlations (*r*): NR
†(Ohlwein et al., 2016) Cross-sectional $PM_{2.5}$: 2008-2009 Baseline: 2007/10	SALIA N = 402 Women, 69-79 yrs	LUR at residence Model fit R_2 = 0.88, cross-validation R_2 = 0.79	Median: 17.4 (IQR: 16.9-18.8)	E/E" ratio LAVI (Tissue Doppler)	Copollutant model: NR Copollutant correlations (*r*): *r* = 0.85 for NO_X, *r* = 0.86 for NO_2

Avg = average, CHF = congestive heart failure, E/"E ratio = peak Early diastolic filling velocity/peak Early diastolic mitral annulus velocity, LAVI = left atrial volume index, LVMI = Left ventricular mass index, MESA = Multi Ethnic Study of Atherosclerosis, MRI = magnetic resonance imaging, NR = not reported, RVM = right ventricular mass, RVV = right ventricular volume, SALIA = Study on the Influence of Air Pollution on the Lung.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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No association of long-term exposure to $PM_{2.5}$ with left ventricular mass index LVMI or depressed EF was observed in a cross-sectional analysis of the MESA cohort after adjustment for study center (Van Hee et al., 2009). An increase in RV mass [0.11 g (95%CI: -0.05, 0.27)] was observed in the MESA cohort, in association with long term exposure to $PM_{2.}$ after controlling for site and other covariates, however. Associations with RV end diastolic volume and RV mass/end-diastolic volume ratio were also observed but were attenuated after adjustment for site. A sensitivity analysis showed that the increase in RV mass persisted after adjustment for LV mass, indicating that the findings may be explained by pulmonary vascular damage. D'Souza et al. (2017) found that this increase in RV mass was slightly reduced but remained after adjustment for $PM_{10-2.5}$ and NO_2.

Ohlwein et al. (2016) conducted a cross-sectional analysis of the SALIA cohort to determine the association, using an adjusted means ratio (MR) of long-term $PM_{2.5}$ exposure with diastolic function. Two metrics, E/E' ratio and left atrial volume index (LAVI) were determined. The E/E ratio is the ratio of peak early diastolic filling velocity to peak early diastolic mitral annulus velocity and a value less than eight indicates normal diastolic function. LAVI is an indicator of diastolic function severity and a known predictor for cardiovascular disease. The authors observed that LAVI was increased in association with long-term exposure to $PM_{2.5}$.

In summary, the small number of studies provide evidence supporting a possible relationship between heart failure and $PM_{2.5}$ with the epidemiologic studies of long-term exposure to $PM_{2.5}$ reporting positive associations with HF. An association with RV mass was observed, but no association was with LVM or EF, among MESA participants. A cross-sectional association between $PM_{2.5}$ and increased LAVI was observed in the SALIA cohort.

6.2.5.2 Toxicology Studies of Impaired Heart Function

There were no animal studies in the 2009 PM ISA examining heart failure in response to long-term $PM_{2.5}$ exposure. Since the publication of the 2009 PM ISA, (Aztatzi-Aguilar et al., 2015) reported increased ($p < 0.05$) coronary artery wall thickness and a statistically significant ($p < 0.05$) increase in two genes typically associated with responding to cardiac damage: Acta 1 and Col3a1-. Similarly, Ying et al. (2015) reported that long-term exposure to $PM_{2.5}$ increased ($p < 0.05$) heart weight, and ($p < 0.05$) contractility of aortic rings in response to phenylephrine, while decreasing ($p < 0.05$) stroke volume, and ($p < 0.05$) cardiac output in SH rats. Importantly, these effects were reversible after stopping $PM_{2.5}$ exposure and allowing 5 weeks of recovery time. These authors also found an increase in the cardiac hypertrophic markers Acta1 and Myh7 ($p < 0.05$), but not in Serca2. In an additional study, Wold et al. (2012) reported that relative to controls, mice exposed long-term to $PM_{2.5}$ had a statistically significant increase in heart weight ($p < 0.05$), displayed cardiac remodeling as evidenced by increased diastolic dimensions, and had a statistically significant decrease ($p < 0.05$) in contractility in response to dobutamine, but preserved coronary flow. Cardiac remodeling results were consistent with additional

experiments indicating a statistically significant decrease in ($p < 0.05$) Serca-2 protein levels, increased ($p < 0.05$) myosin heavy chain β protein levels, and increased ($p < 0.05$) collagen expression in whole heart homogenates (Wold et al., 2012). However, in contrast to these studies, Lippmann et al. (2013a) did not find changes in cardiac function measurement following long-term exposure of $APOE^{-/-}$ mice to $PM_{2.5}$ from Manhattan or Tuxedo, NY. Nonetheless, there is evidence across multiple animal toxicological studies demonstrating that long-term exposure to $PM_{2.5}$ may lead to impaired heart function.

Recent studies also highlight that exposure to $PM_{2.5}$ during gestation may result in cardiac dysfunction later in life. Gorr et al. (2014) exposed female mice to $PM_{2.5}$ during pregnancy and while nursing and then assessed cardiac function in offspring. The authors reported that at adulthood, offspring had reduced left ventricular fractioning with greater ventricular systolic diameter ($p < 0.05$), reduced ejection fraction ($p = 0.0005$), and other indicators of cardiac dysfunction when compared to FA control mice. In a follow-up study using a similar exposure scenario, Tanwar et al. (2017) confirmed earlier findings of ventricular dysfunction and also reported collagen deposition, as well as prolonged increased ($p > 0.05$) action potentials in isolated cardiomyocytes. They also measured decreased levels of calcium homeostasis proteins (Serca-2A, NCX, *p*-PLN). Furthermore, work from the same lab, Tanwar et al. (2017) demonstrated that prenatal exposure alone was sufficient to produce heart failure in adulthood, looking at similar outcomes as Gorr et al. (2014). More information on studies published since the 2009 ISA can be found in Table 6-40 below.

Table 6-40 Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and impaired heart function.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per treatment group	Inhalation of 178 μg/m^3 $PM_{2.5}$ from a high traffic and industrial area north of Mexico City in early summer for 5 h/day for 8 weeks (4 days/week).	Coronary artery wall thickness measured in myocardial slices collected 24 h post-exposure Gene expression consistent with cardiac damage in heart tissue collected 24 h post-exposure
(Gorr et al., 2014)	Pregnant (In utero) and neonatal FVB mice offspring	Inhalation of 51.69 μg/m^3 $PM_{2.5}$ CAPS from Columbus, OH, exposures of dams for 6 h/day, 7 days/week, from the day after vaginal plug discovery until weaning of pups. After weaning, mice were exposed to room air until 3 mo old	Birth weight, body and heart weights, end-systolic and end-diastolic ventricular dimensions, fractional shortening and posterior wall thickness. Contraction length and calcium reuptake during relaxation, cardiac collagen content.

Table 6-40 (Continued): Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and impaired heart function.

Study	Study Population	Exposure Details	Endpoints Examined
(Tanwar et al., 2017)	FVB mice, pregnant (in utero) and offspring	In utero inhalation of 73.61 ug/m^3 $PM_{2.5}$ CAPs for 6h/day, 7 days/week throughout pregnancy.	Pressure-volume loop, fractional shortening, left ventricular end-systolic and -diastolic diameter, left ventricular posterior wall thickness, end-systolic elastance, contractile reserve, contractility, collagen deposition, inflammatory response, epigenetic markers 12 week after birth
(Wold et al., 2012)	8 week old C57BL/6 mice, M	Inhalation of 85 µg/m^3 (16.9-266.4 µg/m^3) $PM_{2.5}$, for 6 h/day, 5 days/week, for 9 mo from Columbus, OH	Heart weight, contractility, cardiac remodeling, hypertrophic markers, cardiac fibrosis post exposure
(Ying et al., 2015)	4 week old SH rats, M, n = 6/treatment group	Inhalation of 128.3 ± 60.4 µg/m^3 $PM_{2.5}$ CAPs Exposed 6 h/day, 5 days/week for 15 week from Columbus, OH	Heart weight, contractility of aortic rings, stroke volume and cardiac output post 15 week exposure other exposed rats were not sacrificed in order for stroke volume and cardiac output analysis to be repeated after removal of $PM_{2.5}$ exposure. Hypertrophic markers 15 week post
(Lippmann et al., 2013a) NPACT Study 1	$ApoE^{-/-}$ mice, M, n = 4-8 per treatment group,	CAPs from Tuxedo, NY, Manhattan, NY (136, 123, ug/m^3, respectively) for 6 h/day, 5 days/week for 6 mo	Ejection fraction, fractional shortening, cardiac wall thickness
(Tanwar et al., 2017)		Pregnant FVB mice and their offspring	Exposure to filtered air or Ohio State $PM_{2.5}$ CAPs at an average concentration of 73.61 µg/m^3 for 6 h/day, 7 days/week throughout pregnancy (prenatal only).
			At 12 weeks of age in offspring, echocardiographic assessment of pressure and volume changes in the heart including left ventricular (LV) systolic and diastolic internal dimensions (LVESd and LVEDd) and systolic and diastolic posterior wall thickness (PWTs and PWTd). Percent fractional shortening (%FS). Ca++ flux. Collagen deposition in the heart. Epigenetic modification (Sirt 1 and 2, Dnmt1, 3a and 3b).

$APOE^{-/-}$ = apolipoprotein E null mice, CAPs = concentrated ambient particles, d = day, h = hour, m = male, n = number, SH = spontaneously hypertensive, week = week.

6.2.6 Cardiac Electrophysiology and Arrhythmia

Electrical activity in the heart is typically measured using surface electrocardiography (ECG). ECGs measure electrical activity in the heart due to depolarization and repolarization of the atria and

ventricles (see Section 6.1.4). Atrial fibrillation (AF) is the most common type of arrhythmia. Despite being common, clinical and subclinical forms of AF are associated with reduced functional status, quality of life and is associated with downstream consequences such as ischemic stroke (Prystowsky et al., 1996; Laupacis et al., 1994) and CHF (Roy et al., 2009), contributing to both cardiovascular disease (CVD) and all-cause mortality (Kannel et al., 1983). Ventricular fibrillation is a well-known cause of sudden cardiac death and commonly associated with myocardial infarction, heart failure, cardiomyopathy, and other forms of structural (e.g., valvular) heart disease. Pathophysiologic mechanisms underlying arrhythmia include electrolyte abnormalities, modulation of the ANS, membrane channels, gap junctions, oxidant stress, myocardial stretch and ischemia. Ventricular conduction and repolarization abnormalities such as QRS and QT interval prolongation, their subclinical correlates including left ventricular hypertrophy, and clinical antecedents including hypertension are also associated with cardiac arrest (Rautaharju et al., 1994).

In a study reviewed in the 2009 PM ISA Liao et al. (2009) reported that neither 30- nor 365-day $PM_{2.5}$ concentrations were associated with supraventricular or ventricular ectopy, which are the most frequent forms of arrhythmia in the general population, among women enrolled in the WHI clinical trials. The association between long-term exposure to $PM_{2.5}$ and ventricular repolarization abnormalities was not studied at the time the 2009 PM ISA was published. There are no experimental animal studies and such studies continue to be lacking.

6.2.6.1 Epidemiologic Studies

Several recent studies have examined the association between long-term exposure to $PM_{2.5}$ and arrhythmogenic effects in additional populations (Table 6-41). Atkinson et al. (2013) found that ICD-coded arrhythmias and cardiac arrest were not associated with annual mean $PM_{2.5}$ concentrations. In the REGARDS cohort, O'Neal et al. (2016) examined the cross-sectional association with premature atrial contractions (PACs) and long-term $PM_{2.5}$ exposure reporting [OR: 1.19 (95%CI: 1.05, 1.34)]. Van Hee et al. (2011) examined associations between ventricular conduction, repolarization, and spatiotemporally modeled annual mean $PM_{2.5}$ concentrations of 4,783 MESA participants in six U.S. centers. Consistent with O'Neal et al. (2016), Van Hee et al. (2011) found strong, positive, and ORs for associations between prolonged QRS, prolonged QT, and long-term $PM_{2.5}$ concentrations. The study also found increasing ORs when controlling for study center that were robust to additional control for subclinical atherosclerosis, findings that were presented to support the importance of the study's within-city $PM_{2.5}$ gradients and their atherosclerosis-independent mechanism of ECG effects (Van Hee et al., 2011).

Table 6-41 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and arrhythmia and ventricular conduction.

Study	Study Population	Exposure Assessment	Concentration ($\mu g/m^3$)	Outcome	Copollutants Examined
†Atkinson et al. (2013) U.K. Prospective cohort $PM_{2.5}$: 2002 Follow-up:2003-2007	General Practice database N = 205 practices N = 836,557 patients (40-89)	Annual avg (2002) estimated using dispersion model (1 by 1 km grid) linked to residential postal code $PM_{2.5}$ model validation: R^2 = 0.5 (correlation with national air quality network)	Mean 12.9 (SD 1.4) Range 7.2-20.2 IQR: 1.9	Arrhythmia and cardiac arrest	Copollutant model: NR Copollutant correlations (*r*): PM_{10} *r* = 0.99, SO_2 *r* = 0.53; NO_2 *r* = 0.87; O_3 *r* = -0.43
(Liao et al., 2009) 24 States, U.S.	WHI N = 57,422	30-day and annual avg estimated using log-normal kriging interpolation at geocoded residential address	NR	VE and SVE detected on ECG	Copollutant model: NR Copollutant correlations (*r*): NR
†(O'Neal et al., 2016) Southern states, U.S. Cross-sectional 2003-2007	REGARDS N = 26,609	1-yr avg, MODIS plus ground measurements, 10 x 10 km grid	Mean 13.5 (SD = 1.9)	Premature atrial contraction	Copollutant model: NR Copollutant correlations (*r*): NR
(Van Hee et al., 2009) 6 Communities, U.S. Cross-sectional $PM_{2.5}$: 2000 Baseline exam: 2000-02	MESA N = 6,814	Annual avg $PM_{2.5}$ predictions using hierarchical spatio-temporal model (see (Szpiro et al., 2010)) Root mean square error 0.34-0.94 $\mu g/m^3$	Range in annual avg (1 y prior to outcome) ~12-22	QT prolongation Intraventricular conduction decay (12 lead ECG)	Copollutant model: NR Copollutant correlations (*r*): NR

Avg = average, ICD = International Classification of Disease, MESA = Multiethnic Study of Atherosclerosis, NR = not reported, REGARDS = REasons for Geographic and Racial Differences in Stroke, VE = ventricular ectopy, SVE = supraventricular ectopy, WHI = Women's Health Initiative.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

6.2.7 Blood Pressure and Hypertension

High blood pressure is typically defined as a systolic blood pressure above 140 mm hg or a diastolic blood pressure above 90 mm Hg. Hypertension, the clinically relevant consequence of chronically high blood pressure, typically develops over years. Small population-level changes in blood pressure, even in the absence of clinical hypertension, can have large effects on clinical outcome prevalence (Rose, 1985). Pulse pressure (PP) or the difference between SBP and DBP, as well as mean arterial pressure (MAP), which is a function of cardiac output, systemic vascular resistance and central venous pressure, are additional outcome metrics used in studies of air pollution on blood pressure. Because high blood pressure increases the force on the artery walls the condition can damage the blood vessels and increase risk for cardiovascular disease and stroke. Ventricular remodeling that occurs with hypertension leads to the repolarization abnormalities (see Section 6.2.6) often accompany hypertension and chronic conditions such diabetes and renal disease. Further, hypertension is one of the array of conditions including high blood sugar, excess body fat around waste and abnormal triglycerides that comprise metabolic syndrome (see CHAPTER 7), which is a risk factor for heart disease, stroke and diabetes.

The 2009 PM ISA reviewed a limited number of long-term PM exposure and blood pressure reporting small magnitude effects. The body of literature has grown substantially, and currently includes longitudinal analyses generally showing small magnitude increases in SBP, PP, and MAP in association with long term exposure to $PM_{2.5}$. Recent studies of children did not support an association between long-term $PM_{2.5}$ exposure and blood pressure.

6.2.7.1 Epidemiologic Studies

6.2.7.1.1 Blood Pressure

Several analyses of data from established cohorts, that generally report associations between increasing long-term $PM_{2.5}$ concentration and increasing blood pressure, are available for review (Table 6-42). Hicken et al. (2013) completed blood pressure measurements among 5,570 MESA participants with $PM_{2.5}$ exposure assigned using 30- day averages from all monitors within their MESA site. Chan et al. (2015) examined 43,629 participants from across the United States enrolled in the Sister Study. Both studies showed elevated SBP, PP, and MAP with $PM_{2.5}$ exposures but no effect on DBP. A sensitivity analysis in MESA study using 60-day average $PM_{2.5}$ exposure yielded similar results. Effect sizes reported in these studies were typically small (e.g., SBP: 1.4 (0.4, 1.7) mm hg (Chan et al., 2015); SBP: 0.95 (0.5, 1.4) mm hg (Hicken et al., 2013)). No evidence of modification by race was observed, while associations with blood pressure were higher in the higher income group in MESA (Hicken et al., 2013).

Wellenius et al. (2012b), examined blood pressure changes during an orthostatic challenge of older adult participants in the MOBILIZE study (changes between supine blood pressure and 1- and 3-minute standing blood pressure). Although effects of $PM_{2.5}$ were observed on static supine and standing diastolic blood pressures, no evidence was found to indicate that $PM_{2.5}$ exposure over the previous 28 days influences the change in blood pressure that occurs between supine and standing states. By contrast, the pooled analysis of 12 European cohorts from ESCAPE, reported null effects of $PM_{2.5}$ for both systolic and diastolic blood pressure (Fuks et al., 2014). Study-specific estimates were variable in magnitude and direction (Fuks et al., 2014). Meta-analyzed associations reported in the ESCAPE study were strengthened after adjustment for NO_2.

Table 6-42 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and blood pressure in adults.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome(s)	Copollutants Examined
†(Hicken et al., 2013) Cross-sectional $PM_{2.5}$: 2002 Outcome: 2000-2002	MESA N = 6,814 45-85 yrs	1 mo avg prior to exam estimated from daily monitor avg	NR	Mean difference in SBP, DBP, PP and MAP	Copollutant models: NR Copollutant correlations (*r*): NR
†(Chan et al., 2015) Cross-sectional $PM_{2.5}$: 2006 Outcome: 2003/09	Sister Study N = 43,629 35-76 yrs	Annual avg at residential address estimated kriging interpolation incorporating satellite observations of AOD, see (Sampson et al., 2013)C-V R^2 = 0.88	Nationwide IQR: 8.8-12.4 (regional distribution in Fig 2)	SBP, DBP, PP, MAP	Copollutant models: NR Copollutant correlations (*r*): NR
†(Wellenius et al., 2012b) $PM_{2.5}$: 2005-2008 Outcome: 2005-2008	MOBILIZE Boston N = 747 ≥70 yrs	28 d avg of daily measurements within 10 km of clinic and 20 km of participants' residence	Mean: 8.6 IQR: 4.9	Change in SBP, DBP, supine SBP, supine DBP	Copollutant models: NR Copollutant correlations (*r*): NR

Table 6-42 (Continued): Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and blood pressure in adults.

Study	Study Population	Exposure Assessment	Concentration µg/m³	Outcome(s)	Copollutants Examined
†(Fuks et al., 2014) 15 Cohorts, 9 Countries, Europe Outcome: 1990-2000 $PM_{2.5}$: 2008-2011 (Fuks et al., 2011)	ESCAPE N = 164,484	Annual avg estimated using LUR residential address See (Eeftens et al., 2012) Mean model fit R^2 = 0.71	Mean: 12 (range of means: 6.6-18.4)	Blood pressure Hypertension Intake of BP lowering medication	Copollutant correlations (*r*): $PM_{2.5}$ absorbance *r* = 0.47-0.99 $PM_{10-2.5}$ *r* = .02-0.77 BI2 *r* = 0.19-0.75 (range depends on study area) Copollutant models adjusted for NO_2, traffic noise

Avg = average, AOD = Aerosol Optical Density, BP = blood pressure, C-V = cross validated, DBP = Diastolic Blood Pressure, ESCAPE = European Study of Cohorts for Air Pollution Exposure, LUR = land use regression, MAP = Mean Arterial Pressure, MESA = Multi-ethnic study of Atherosclerosis, MOBILIZE = Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston, N, n = number of subjects, NR = not reported, PP = Pulse Pressure, SBP = Systolic Blood Pressure

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Children

Studies (Table 6-43) examining long term $PM_{2.5}$ exposure and blood pressure among children (Bilenko et al., 2015a; Bilenko et al., 2015b; Liu et al., 2014a) were completed in the United States and Europe. A study of newborns in Massachusetts found elevated SBP with higher $PM_{2.5}$ averages over the 30-, but not 60- or 90-day periods before birth (van Rossem et al., 2015) while trimester specific associations between $PM_{2.5}$ and increased SBP increased but confidence intervals were wide [$\beta = 0.66$ (95%CI: -1.31, 2.62)]. The three studies of annual $PM_{2.5}$ exposure conducted in European countries among 10- and 12-year olds (Bilenko et al., 2015a; Bilenko et al., 2015b; Liu et al., 2014a) did not provide evidence supporting an association between long-term $PM_{2.5}$ exposure and increased blood pressure in children. Both small increases and small decreases were observed in these studies.

Table 6-43 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and blood pressure in children.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome(s)	Copollutants Examined
†van Rossem et al. (2015) 1999-2002 1st prenatal visit $PM_{2.5}$ 2000-2008	Project Viva N = 1,131 mother-infant pairs	Spatiotemporal models including satellite observations of AOD, 10 x 10 km grid linked to residence, out of sample R^2 0.87 Temporal model using a fixed-site monitor, reside within 40 km	90 day median 11.8; IQR = 2.3 (spatiotemporal) 90 day median 10.9; IQR = 2 (temporal)	Newborn blood pressure	Copollutant model: NR Copollutant Correlations (*r*): 0.5 BC 0.41 NO_2 0.20 NO_X 0.20 03 0.29 CO
†Liu et al. (2014a) Munich, Leipzig, Wesel, Germany $PM_{2.5}$: 2008-2009	GINIplus LISAplus N = 2,368 10 yrs old	Annual avg estimated at residence using LUR See (Eeftens et al., 2012)	Mean 14.88 (IQR: 4.07)	SBP DBP	Copollutant model: NR Copollutant Correlations (*r*): NR
†Bilenko et al. (2015a) $PM_{2.5}$: Feb 2009-Feb 2010 Outcome: concurrent (12 yr after recruitment 1996/97)	PIAMA N = 1,147 Children 12 yrs	Annual avg estimated at residence (birth and concurrently with exam) using LUR	Mean 16.3 (IQR: 1.2)	SPB DBP	Copollutant model: NR Copollutant Correlations (*r*): NR
†Bilenko et al. (2015b) Cross-sectional $PM_{2.5}$: Feb 2009-Feb 2010 Outcome: concurrent (12 yr after recruitment 1996/97)	PIAMA N = 1,432 12 yrs old	Annual avg estimated at residence (birth and concurrently with exam) using LUR See (de Hoogh et al., 2013)	Median: 16.5 (IQR: 1.2)	SPB DBP	Copollutant model: NR Copollutant Correlations (*r*): 0.67 noise, 0.82 $PM_{2.5}$ abs

Avg = average, AOD = aerosol optical density, DBP = diastolic blood pressure, GINIplus: German Infant Nutritional Intervention plus environmental and genetic influences on allergy development, LISAplus: lifestyle related factors on the Immune System and Development of Allergies in Childhood Study, LUR = land use regression, MOBILIZE = Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston, NR = not reported, N, n = number of subjects, PIAMA = Prevention and Incidence of Asthma and Mite Allergy study, SBP = systolic blood pressure

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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6.2.7.1.2 Hypertension

Prospective studies of the association between long-term exposure to PM2.5 and hypertension are described in Table 6-44. Zhang et al. (2016) conducted a prospective analysis of long-term exposure to $PM_{2.5}$ and self-reported hypertension among women enrolled in the NHS. A positive association of incident hypertension with annual average $PM_{2.5}$ exposure was reported [HR: 1.02 (95%CI: 1.00, 1.03)]. By contrast Coogan et al. (2016) reported no association between long-term $PM_{2.5}$ exposure and hypertension in the Black Women's Health Study (BWHS) [HR: 0.98 (95%CI: 0.88, 1.11)]. This finding, which was based on a refined spatiotemporal exposure model and included additional years of follow-up, supersedes the earlier report indicating a large but imprecise association with hypertension in this cohort [HR: 1.22 (95%CI: 0.97, 1.52)] (Coogan et al., 2012). The largest study of incident hypertension, conducted within a population-based sample of Ontario, Canada residents, reported a fully adjusted HR of 1.07 (95% CI: 1.03, 1.11) (Chen et al., 2014a). This study used the Ontario hypertension database to classify hypertension, including those with at least one hospital admission with a diagnosis of hypertension or two physician claims for hypertension within a two-year period. Larger magnitude associations were reported among participants with diabetes [HR: 1.23 (95%CI: 1.04, 1.46) vs. 1.05 (95%CI: 1.01, 1.10) among those without diabetes]. There was no statistical evidence of modification by other factors (i.e., age, sex, BMI, education, smoking and COPD). Results of Chen et al. (2014a) that pertain to the shape of the C-*R* function are discussed in Section 6.2.16.

Several additional studies examine the cross-sectional association between long-term $PM_{2.5}$ exposure and hypertension (To et al., 2015; Babisch et al., 2014; Fuks et al., 2014; Johnson and Parker, 2009). These cross-sectional studies generally provide support for an association between long-term exposure to $PM_{2.5}$ and the prevalence of hypertension.

Table 6-44 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and hypertension.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome(s)	Copollutants Examined
†(Zhang et al., 2016) Prospective cohort $PM_{2.5}$: 1998-2007 Outcome: 1988-2008	NHS N = 74,880	Time varying annual avg estimated to compute 24-mo and cumulative avg using spatiotemporal models (1 x 1 km grid) C-V R^2 = 0.58 See (Yanosky et al., 2014)	Mean: 15.61	Hypertension SBP/DBP≥140/90 mm hg	$PM_{10-2.5}$ r = 0.37 Copollutant model adjusted for $PM_{10-2.5}$
†(Coogan et al., 2016) Prospective cohort $PM_{2.5}$: 1995-2009 Follow-up: 1995-2011	BWHS N = 9,579 black women free of hypertension at baseline (21-69 yrs)	LUR and BME in spatiotemporal model, exposure assigned at residence	Mean 13.9 IQR: 2.9	Self-report of doctor diagnosed Hypertension and concurrent use of antihypertensive medication	Copollutant model: NR Copollutant Correlations (r): NR
†(Chen et al., 2014a) Ontario, Canada Prospective cohort $PM_{2.5}$: 2001-2006 Outcome: 1996/2005 – Dec 2010	Ontario Hypertension Database N = 79,942 ≥35 yrs (baseline)	Annual avg at postal code estimated using satellite observations of AOD	Mean 10.7 (range 2.9-19.2)	Hypertension registry (ICD diagnostic codes 401-405, ICD10 I10-I13/15)	Copollutant model: NR Copollutant Correlations (r): NR

Avg = average, AOD = aerosol optical density, BME=Bayesian maximum entropy, BWHS = Black Women's Health Study, C-V=cross-validation, ICD=international classification of disease, IDW = inverse distance weighted, km=kilometer, LUR = land use regression, NHS = Nurses' Health Study.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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In summary, this expanded body of literature provides evidence of association between long-term $PM_{2.5}$ exposure, blood pressure, and hypertension, although consistency of associations varied with the specific outcome and averaging times examined. Limited evidence from studies of adult blood pressure indicated increases in systolic and diastolic blood pressure (SBP, DBP) as well as pulse pressure (PP) and mean arterial pressure (MAP) 28 to 60-day average exposures. Studies of children did not consistently report associations of between long-term exposures of months to years and increased blood pressure.

6.2.7.1.3 Gestational Hypertension and Preeclampsia

Epidemiologic studies examining increases in $PM_{2.5}$ concentrations and hypertensive disorders of pregnancy, including preeclampsia, are discussed in detail in Section 9.2.1. Overall, these do not observe consistent results. The methods by which exposure was assigned in these studies may contribute to the heterogeneity in associations observed across these studies. For example, the association between a composite outcome of gestational hypertensive disorders and $PM_{2.5}$ changed based on how concentrations were determined in a study conducted in California (Wu et al., 2011; Wu et al., 2009). However, two meta-analyses have estimated positive odds ratios (ORs 1.15-1.47) for $PM_{2.5}$ and preeclampsia, however both had large heterogeneity scores, and therefore a combined effect may be inappropriate (Hu et al., 2014; Pedersen et al., 2014).

6.2.7.1.4 Renal Function

Observed effects of long-term $PM_{2.5}$ exposure on renal function may be secondary to hypertension because chronic increases in vascular pressure can contribute to glomerular and renal vasculature injury, which can lead to progressive renal dysfunction. The relationship between BP and renal function is complicated, however, because hypertension contributes to renal dysfunction but damage to the kidneys can also cause increased BP. The 2009 PM ISA did not review studies of the association between long-term exposure to $PM_{2.5}$ and renal function. The literature remains limited but an epidemiologic study of older adult males in the NAS, Mehta et al. (2016) reported an association between annual average $PM_{2.5}$ exposure and lower estimated glomerular filtration rate (eGFR) (-4.45 mL/min/1.73 m^2 [95%CI: -7.12, -1.81]). A longitudinal decrease was also observed as a per year reduction in eGFR in this study.

6.2.7.2 Toxicology Studies of Changes in Blood Pressure (BP)

In the current ISA, studies using rats have demonstrated increased ($p < 0.05$) blood pressure in response to long-term $PM_{2.5}$ exposure. Aztatzi-Aguilar et al. (2016) exposed adult male Sprague–Dawley rats to Mexico City fine CAPS and measured BP on the 4th day of each weekly exposure for 8 weeks.

The mean arterial pressure (MAP) was calculated and found to be increased ($p < 0.05$) at weeks 1, 5, and 8. In an additional study, Ying et al. (2015) identified that long-term CAPs exposure increased ($p < 0.05$) BP in SH rats compared to filtered air controls. This increase in BP persisted throughout the 15-week exposure, but returned to baseline two weeks after $PM_{2.5}$ was withdrawn. Furthermore, Wold et al. (2012) found that relative to controls, mice exposed long-term to $PM_{2.5}$ had a statistically significant increase in SBP, DBP, and MAP, while pulse pressure decreased relative to controls ($p > 0.05$). In summary, these studies individually and collectively support that long term $PM_{2.5}$ exposure can increase BP. More information on studies published since the 2009 ISA can be found in Table 6-45 below.

6.2.7.2.1 Renin-Angiotensin System

As noted above (see Section 6.1.6.4.1), the renin-angiotensin system can have direct effects on changes in blood pressure. Since the publication of the 2009 PM ISA, additional studies have evaluated the effects of PM on this system. Long-term $PM_{2.5}$ exposure resulted in a statistically significant increase ($p < 0.05$) in At1r and B1r mRNA levels in rat heart tissue, whereas At2r, and ACE were not appreciably changed (Aztatzi-Aguilar et al., 2015). In a follow-up study, Aztatzi-Aguilar et al. (2016) found that in rat kidney tissue, although mRNA levels of Ace and At1r statistically significantly decreased at 8 weeks post exposure ($p > 0.05$), protein levels statistically significantly increased ($p < 0.05$) relative to controls. In addition, the authors also reported that B1r mRNA and protein was statistically significantly ($p < 0.05$) higher following long-term $PM_{2.5}$ exposure. Thus, there is evidence that long-term $PM_{2.5}$ exposure can result in the types of changes in the renin-angiotensin system that could lead to changes in blood pressure.

Table 6-45 Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and blood pressure (BP).

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per treatment group	Inhalation of 178 µg/m^3 $PM_{2.5}$ from a high traffic and industrial area north of Mexico City in early summer for 5 h/day for 8 weeks (4 days/week).	Angiotensin and bradykinin system gene and protein expression in heart tissue post exposure
(Aztatzi-Aguilar et al., 2016)	Sprague Dawley rats, M, n = 12/group	Inhalation of 375 µg/m^3 $PM_{2.5}$ CAPs, 5 h/day, 4 day/week, for 8 week from Mexico City	Mean blood pressure on the 4th day of each weekly exposure for 8 weeks Angiotensin and bradykinin system gene and protein expression in kidney tissue post exposure
(Ying et al., 2015)	4 week old male SH rats, n = 6/group	Inhalation of 128.3 ± 60.4 µg/m^3 $PM_{2.5}$ CAPs for 6 h/day, 5 days/week for 15 weeks from Columbus, OH	SBP measured weekly during exposure
(Wold et al., 2012)	8 week old C57BL/6 mice, M	Inhalation of 85 µg/m^3 (16.9-266.4 µg/m^3) $PM_{2.5}$, for 6 h/day, 5 days/week, for 9 mo from Columbus, OH	SBP, DBP, and MAP recorded daily for 3 days post exposure

BP = blood pressure, CAP = concentrated ambient particle, d = day, h = hour, m = male, n = number, SBP = systolic blood pressure, week = week

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6.2.8 Peripheral Vascular Disease (PVD), Venous Thromboembolism, Pulmonary Embolism

2 Thrombosis refers to intravascular formation of a blood clot inside the blood vessel. The clot can
3 form an embolism that moves from its point of origin to a distant vessel where it can become lodged and
4 occlude blood flow. Thrombi typically form in the deep (i.e., popliteal, femoral, iliac) veins of the lower
5 extremities and can give rise to emboli that lodge in the pulmonary arteries. Deep vein thromboses
6 (DVTs) and pulmonary emboli (PE) are the most common subtypes of venous thromboembolism (VTE).
7 Although no studies of $PM_{2.5}$ were in the 2009 PM ISA, a case-control study reported an association
8 between PM_{10} exposure and risk of deep vein thrombosis (DVT) (Baccarelli et al., 2008). Recent
9 longitudinal analyses of report inconsistent results regarding the association of long-term exposure to
10 $PM_{2.5}$ and VTE.

6.2.8.1 Epidemiologic Studies

Following the DVT study of Baccarelli et al. (2008), longitudinal analyses of the WHI (Shih et al., 2011) and the NHS (Pun et al., 2015) examined other $PM_{2.5}$ in relation to VTE. Shih et al. (2011) found no evidence of association with VTE [HR: 0.96 (95%CI: 0.73, 1.26)], nor did they find evidence of an interaction with hormone therapy as did Baccarelli et al. (2008). By contrast, Pun et al. (2015) reported a positive association [HR: 1.11 (95%CI: 1.00, 1.24)] among women in the NHS. VTE events are uncommon, especially in women with and without established risk factors for VTE and its subtypes. Overall, the evidence remains limited (Table 6-46).

Table 6-46 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and thromboembolism.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
†Shih et al. (2011) 40 Centers, U.S. Prospective cohort $PM_{2.5}$: 1999-2004 Follow-up: 1993/98 -2004	WHI Post-menopausal women with no history of DVT N = 26,450 Mean follow-up 7.7 yrs	Annual avg estimated using kriging interpolation at geocoded residential address	Mean: 13.4	Physician adjudicated DVT	Copollutant model: NR Copollutant Correlations (*r*): NR
†Pun et al. (2015) 11 States, U.S. $PM_{2.5}$: 1988-2007 Follow-up 1992-2008	NHS	Annual avg estimated using spatiotemporal model at residential address C-V regression slope = 0.87, error 1.81 µg/m^3	Mean: 12.6 IQR: 4.1	Self-reported diagnosis of PE confirmed by physician medical record review	Copollutant model: NR Copollutant Correlations (*r*): NR

Avg = average, C-V = cross validation, DVT = deep vein thrombosis, NHS = Nurses' Health Study, PE = Pulmonary Embolism, WHI = Women's Health Initiative.
†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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6.2.9 Aggregated Clinical Cardiovascular Outcomes

Several studies define outcome categories that aggregate across specific types of cardiovascular and cerebrovascular disease (CVD and CBVD) (Table 6-47). The outcomes, variously defined and combined, include MI, angina, atherosclerosis, aneurysm, chronic and acute ischemic heart disease, stroke or other cerebrovascular disease, coronary heart disease, heart failure, cardiac arrest, arterial embolism and thrombosis, and peripheral vascular disease, as well as relevant procedures such as revascularization, angioplasty, bypass, or cardiac device implants. Associations of long-term exposure to $PM_{2.5}$ with such aggregated clinical outcomes are presented here with an emphasis on studies that leverage large sample sizes and numbers of events within aggregated outcome groupings to conduct stratified analyses.

The analysis of post-menopausal women enrolled in WHI Miller et al. (2007) was described in the 2009 PM ISA and reported an association of long-term exposure to $PM_{2.5}$ and coronary events, including MI, revascularization and death from CHD, of 1.11 (95%CI: 1.04, 1.19). Recent studies continue to strengthen the evidence supporting an effect of long-term exposure $PM_{2.5}$ on aggregated cardiovascular outcomes. In a follow-up WHI analysis Chi et al. (2016a) examined modification by individual and neighborhood-level socioeconomic status (SES) to determine if these factors could explain the findings of Miller et al. (2007). Authors found that the association was not attenuated after adjustment for SES indicators [HR: 1.14 (95% CI: 1.02, 1.27)]. Although individual SES did not modify the association between long-term exposure to $PM_{2.5}$ and CVD, there was statistical evidence of modification by neighborhood SES. The strongest association was found in most disadvantaged neighborhood SES group [HR: 1.39 (95% CI: 1.21, 1.61)] with a null association in the least disadvantaged neighborhood SES group [HR: 0.90 (95%CI: 0.72, 1.07)].

In an analysis of data from Medicare recipients across the U.S. Makar et al. (2017) examined the association of 2-year $PM_{2.5}$ concentrations with hospital admissions for diseases of the circulatory system among those with annual average concentrations less than 12 $\mu g/m^3$. Authors found an increase in circulatory system hospital admissions [HR: 1.06 (95%CI: 1.02, 1.09), cutpoint of 12 $\mu g/m^3$ and [HR: 1.18 (95% CI 1.10, 1.27) cutpoint of 8 $\mu g/m^3$]. Positive associations between long-term exposure to $PM_{2.5}$ and cardiovascular disease were reported in cross-sectional studies (Feng and Yang, 2012; Johnson and Parker, 2009).

In summary, these studies generally support an effect of long-term exposure $PM_{2.5}$ on a variety of pooled cardiovascular outcomes. These studies are generally large, allowing stratified analyses. Findings of Feng and Yang (2012) and Hart et al. (2015b) related to regional differences in the association between long-term exposure to $PM_{2.5}$ and CVDs are discussed in Section 6.2.17.

Table 6-47 Characteristics of the studies examining the association between long-term $PM_{2.5}$ exposures and cardiovascular diseases.

Study	Study Population	Exposure Assessment	Concentration µg/m^3	Outcome	Copollutants Examined
Miller et al. (2007) 36 metro areas, U.S. Prospective cohort $PM_{2.5}$: 2000 Follow-up: 1994/98-2002	WHI observational cohort N = 65,893 Median follow-up: 6 yrs	Annual avg of closest monitor (2000) within 10 km of monitor	Median 13.4 IQR 11.6-18.3	CVD event (MI, revascularization, stroke, death from CHD, CBVD) Medical record review by physician adjudicators	Copollutant model: NR Copollutant correlations: NR
†(Chi et al., 2016a) 36 metro areas, U.S. Prospective cohort $PM_{2.5}$: 2000 Follow-up: 1994/98-2005	WHI observational cohort Post-menopausal women 50-79 yrs N = 51,754 Mean follow-up 7.6 yrs	Annual avg (2000) kriging interpolation to estimate concentration at residential address C-V R^2 = 0.88 (Sampson et al., 2013)	Mean: 12.7 (SD: 2.9) IQR: 4.1	CVD Event (MI, stroke, death from CHD or CBVD)	Copollutant model: NR Copollutant correlations: NR
†Makar et al. (2017) Prospective cohort $PM_{2.5}$: 2000-2010 Outcome: 2002-2010	Medicare N = 32,119 MCBS survey participants 65+yrs	Spatiotemporal model incorporating satellite observations of AOD over a 1 x 1 km grid for entire US C-V R^2 = 0.84	Full Cohort Mean: 12 IQR: 3.41 Low pollution cohort Mean: 10.18 IQR: 2.46	Circulatory system HA ICD9: 390-459	Copollutant model: NR Copollutant correlations: NR

Avg = average, CVD = cardiovascular disease, CHD = coronary heart disease, CBVD = cerebrovascular disease, C-V = cross validation, hospital admissions = hospital admission, ICD = International Classification of Disease, MCBS = Medicare current beneficiary survey, MI = myocardial infarction, N, n = number of subjects, NR = not reported, WHI = Women's Health Initiative.

†Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

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6.2.10 Long-Term $PM_{2.5}$ Exposure and Cardiovascular Mortality

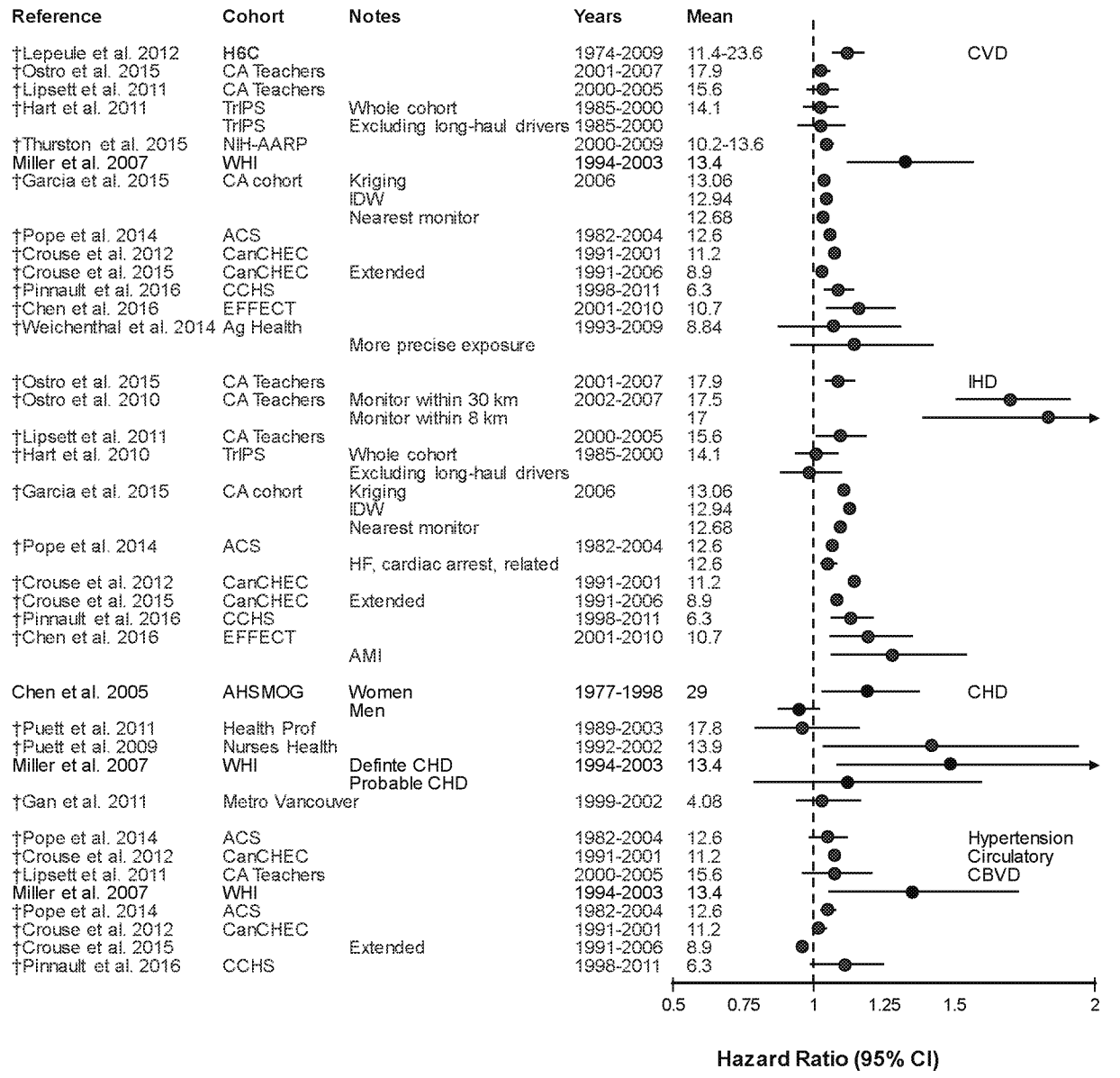
Studies that examine the association between long-term $PM_{2.5}$ exposure and cause-specific mortality outcomes, such as cardiovascular mortality, provide additional evidence for $PM_{2.5}$-related cardiovascular effects, specifically whether there is evidence of an overall continuum of effects. Evidence from studies of long-term $PM_{2.5}$ exposure and mortality are presented in detail in Section 6.2.10 evidence from studies investigating cardiovascular mortality provided some of the strongest evidence for a cardiovascular effect related to long-term $PM_{2.5}$ exposure in the 2009 PM ISA (U.S. EPA, 2009) and are summarized here to inform the effect of long-term $PM_{2.5}$ exposure on the continuum of cardiovascular health effects. The 2009 PM ISA (U.S. EPA, 2009) included evidence from a number multicity U.S. studies, including the American Cancer Society (ACS) cohort (Pope III et al., 2004), the Harvard six cities cohort (Laden et al., 2006), the Women's Health Initiative (WHI) (Miller et al., 2007), and the Seventh-Day Adventist (AHSMOG) cohort (Chen et al., 2005). These studies continue to provide strong support for the relationship between long-term exposure to $PM_{2.5}$ and cardiovascular mortality. In addition, extended analyses of the ACS and Harvard Six Cities studies, as well as results from recent cohort studies contribute to the body of evidence for this relationship (Figure 6-19).

Pope et al. (2014) and Turner et al. (2016) used the extended follow-up period of the ACS to examine the associations between long-term $PM_{2.5}$ exposure and cardiovascular, ischemic heart disease, heart failure and cardiac arrest, cerebrovascular disease, and hypertensive disease. The results of these extended analyses were consistent with previous results from the ACS cohort for cardiovascular and ischemic heart disease. In addition, these extended analyses provide associations for causes of death that had previously not been evaluated among the ACS cohort. Positive associations were observed with heart failure and cardiac arrest, cerebrovascular disease, and hypertensive disorder. Lepeule et al. (2012) reported the results of an extended analysis of the Harvard Six Cities cohort, extending the follow-up period to include deaths between 1974 and 2009, and the strong association with cardiovascular mortality persisted.

A recent series of studies conducted in Canada linked census data with data from the Canadian Mortality Database to create the Canadian Census Health Environment Cohort (CanCHEC) and evaluated the relationship between long-term $PM_{2.5}$ exposure and CVD (including IHD, CBVD, and circulatory) mortality. The authors observed positive associations between CVD mortality and long-term $PM_{2.5}$ exposure, with similar estimates for satellite-derived estimates and ground monitor estimates. The strongest association was for IHD mortality and the weakest was for cerebrovascular mortality (Figure 6-19). (Chen et al., 2016) limited their analyses to CanCHEC cohort participants residing in Ontario who had experienced an acute myocardial infarction, and observed positive associations with CVD, and IHD deaths, as well as deaths due to subsequent acute myocardial infarctions. Crouse et al. (2015) extended the follow-up period of the CanCHEC cohort to include five additional years (1991-2006) and observed positive associations for cardiovascular mortality, with the strongest association observed between long-

term exposure to $PM_{2.5}$ and mortality due to diabetes, followed by IHD. The association for cerebrovascular mortality was just below the null value. The general pattern and magnitude of these associations were generally unchanged in cumulative risk models that include O_3 and/or NO_2. Weichenthal et al. (2016a) evaluated the subset of the CanCHEC cohort living within 5 km of a ground monitor (n = 193,300) and observed associations with IHD mortality that were close to the null value.

Several recent U.S. cohort studies examined the association between long-term $PM_{2.5}$ exposure and cardiovascular mortality. The California Teachers Study (Lipsett et al., 2011; Ostro et al., 2010) observed positive associations between long-term $PM_{2.5}$ exposure and IHD and cerebrovascular mortality, with the strongest association observed with IHD (HR: 1.70; 95% CI: 1.51, 1.91 per 5.0 $\mu g/m^3$ increase in long-term $PM_{2.5}$ concentration). Analyses restricted to post-menopausal women yielded results similar to those for all subjects. Puett et al. (2009) examined the association between long-term $PM_{2.5}$ exposure and all-cause mortality among a cohort of female nurses in the Nurses' Health Study. The authors observed positive associations with CHD mortality (HR: 1.42, 95% CI: 1.03-1.94). Using a design like that of the Nurses' Health Study, Puett et al. (2011) investigated the effect of long-term $PM_{2.5}$ exposure and mortality among men enrolled in the Health Professionals Follow-up Study cohort. Near null associations were observed for CHD mortality in this cohort. Hart et al. (2011) examined the association between residential exposure to $PM_{2.5}$ and mortality among men in the U.S. trucking industry in the Trucking Industry Particle Study (TrIPS) and observed a modest positive association with cardiovascular mortality.



Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates; horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black text and circles represent evidence included in the 2009 PM ISA; red text and circles represent recent evidence not considered in previous ISAs or AQCDs. Study results from Lepeule et al. (2012) are representative of results from the Harvard Six Cities Cohort; Study results from Pope et al. (2014) are representative of the results from the American Cancer Society Cohort. For complete results from these two cohorts, see Figures 1 and 2. IQR: interquartile range; CVD: cardiovascular disease; IHD: ischemic heart disease; CHD: coronary heart disease; CBVD: cerebrovascular disease; H6C: Harvard Six Cities cohort; TrIPS: Trucking Industry Particle Study; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet & Health Cohort; WHI: Women's Health Initiative; ACS: American Cancer Society Cohort; IDW: inverse distance weighting; HF: heart failure; CCHS: Canadian Community Health Survey; EFFECT: Enhanced Feedback For Effective Cardiac Treatment; AMI: acute myocardial infarction. †Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Figure 6-19 Associations between long-term exposure to $PM_{2.5}$ and cardiovascular mortality in recent North American cohorts.

The magnitude of the associations for long-term $PM_{2.5}$ exposure and cardiovascular mortality among women (Hart et al., 2015a; Lipsett et al., 2011; Ostro et al., 2010; Puett et al., 2009) was higher than those observed in many of the other North American cohorts of men or men and women combined, but similar to that observed by Miller et al. (2007), who also evaluated fatal CHD events among a cohort of post-menopausal women. Several studies that included cohorts of both men and women conducted stratified analyses to see if there was a difference in the association based on sex. Thurston et al. (2015) observed no difference between men and women when examining cardiovascular mortality. Weichenthal et al. (2014b) and (Pinault et al., 2016) reported slightly higher associations with men compared to women, while Beelen et al. (2014) observed higher associations compared among women compared to men. It is unclear why cohort studies that include only women tend to observe higher associations between long-term exposure to $PM_{2.5}$ and cardiovascular mortality compared to other cohorts, and that when cohorts that include both men and women are stratified by sex, the higher association among women is much less consistent.

Overall, the results of these recent U.S. and Canadian cohort studies demonstrate a consistent, positive association between long-term $PM_{2.5}$ exposure and cardiovascular mortality across various spatial extents, exposure assessment techniques, and statistical techniques, and locations, where mean annual average concentrations are $\leq$12 $\mu g/m^3$ (see CHAPTER 11 for study details related to exposure assessment and statistical methods). Additional cohort studies conducted in Europe observed similarly consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality (see Table 11-6 in Section 11.2.2.2), and support the evidence from the U.S. and Canada. Particularly noteworthy is a study conducted in Europe that combined data from 22 existing cohort studies and evaluated the association between long-term $PM_{2.5}$ exposure and cardiovascular (Beelen et al., 2014) mortality. Generally, the associations for cardiovascular mortality were near the null value, except for the subset of cardiovascular deaths attributable to cerebrovascular disease (HR: 1.21, 95% CI: 0.87, 1.69 per 5 $\mu g/m^3$ increase in $PM_{2.5}$) (Beelen et al., 2014).

6.2.11 Heart Rate (HR) and Heart Rate Variability (HRV)

Heart rate variability (HRV) represents the degree of difference in the inter-beat intervals of successive heartbeats, and is an indicator of the balance between the sympathetic and parasympathetic arms of the autonomic nervous system. Heart rate (HR) is modulated at the sinoatrial node by both parasympathetic and sympathetic branches of the autonomic nervous system (see Section 6.1.10).

6.2.11.1 Epidemiologic Studies of Heart Rate Variability (HRV)

Most studies have focused on the association between short-term PM exposure and HRV (see Section 6.1.10). There were no studies of the association between long-term PM exposure and HRV

in the 2009 PM ISA (U.S. EPA, 2009). In a recent study, Park et al. (2010) examined the long-term $PM_{2.5}$-HRV association. Thirty- to 60-day mean $PM_{2.5}$ concentrations from the closest monitor with available data were assigned to geocoded addresses of MESA cohort participants at the baseline cohort exam (2000-2002). Although some inverse HRV-$PM_{2.5}$ associations were observed in the population, overall, the evidence of decreased HRV (i.e., rMSSD, SDNN) was stronger among MESA participants with metabolic syndrome than without metabolic syndrome. Such $PM_{2.5}$-associated decreases in HRV are thought to be harmful given that reduced HRV is a risk factor for cardiovascular disease. This finding in MESA is consistent with that of Whitsel et al. (2009) who reported an inverse association between long-term PM_{10} exposure and HRV that was stronger among those with impaired glucose metabolism (IGM) enrolled in the WHI clinical trial studies.

6.2.11.2 Toxicological Studies of Heart Rate (HR) and Heart Rate Variability (HRV)

In the 2009 PM ISA, long term effects of $PM_{2.5}$ exposure on HRV and HR were not reported. Since the publication of the last review, the HEI NPACT study (Lippmann et al., 2013a) examined the effects of long-term $PM_{2.5}$ exposure from five airsheds (Tuxedo, NY; Manhattan, NY; E Lansing, MI; Seattle, WA and Irvine, CA) on measures of HRV in $APOE^{-/-}$ mice. These authors estimated by fitted curve a statistically significant increases in HR in Manhattan, NY for the first 50 days of the experiment that gradually decreased over the rest of the study. In contrast, using the same methodology, the authors estimated a statistically significant decrease in HR in Tuxedo, NY after 75 days. There were no statistically significant chronic changes in HR at other locations. In an additional study, Wold et al. (2012) reported that long term $PM_{2.5}$ exposure increased HR in SH rats. With respect to HRV, no changes were associated with chronic $PM_{2.5}$ exposure at any location in the NPACT study (Lippmann et al., 2013a). Thus, there is some evidence from animal toxicological studies for changes in HR, but not HRV following long-term exposure to $PM_{2.5}$. More information on studies published since the 2009 ISA can be found in Table 6-48 below.

Table 6-48 Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and heart rate (HR) and heart rate variability (HRV).

Study	Study Population	Exposure Details	Endpoints Examined
(Lippmann et al., 2013a) NPACT Study 1	$ApoE^{-/-}$ mice, M, n = 4-8 per treatment group,	CAPs from Irvine, CA; Tuxedo, NY; Manhattan, NY, Lansing, MI; or Seattle, WA (138, 136, 123, 68, or 60 $\mu g/m^3$, respectively) for 6 h/day, 5 days/week for 6 mo	HR HRV time and frequency domains
(Wold et al., 2012)	8 week old C57BL/6 mice, M	Inhalation of 85 $\mu g/m^3$ (16.9-266.4 $\mu g/m^3$) $PM_{2.5}$, for 6 h/day, 5 days/week, for 9 mo from Columbus, OH	HR post exposure

$APOE^{-/-}$ = apolipoprotein E null mice n = number, h = hour, CAP = concentrated ambient particle, HR = heart rate, HRV = heart rate variability.

6.2.12 Systemic Inflammation and Oxidative Stress

Chronic systemic inflammation is known to affect the vascular system, potentially leading to thrombosis, plaque rupture, MI and stroke, metabolic effects, as well as effects in other organ systems (e.g., central nervous and reproductive systems). Systemic inflammation is associated with changes in the acute phase response, circulating white blood cells, pro-coagulation effects, and endothelial dysfunction. The epidemiologic studies that were reviewed in the 2009 ISA were limited to a cross-sectional study of the association of long-term exposure to PM_{10} with inflammation and coagulation and ecological studies of hematologic measures that could potentially provide insight into oxygen carrying capacity, viscosity and pro-coagulant potential of the blood (U.S. EPA, 2009). Recent longitudinal analyses that consider the time-dependent nature of pulmonary and systemic inflammatory responses have been conducted, and generally show effects on markers of inflammation. Recent experimental studies also add to the evidence reviewed in the 2009 PM ISA that demonstrated inflammatory effects in animals.

6.2.12.1 Epidemiologic Studies

Several studies of long-term $PM_{2.5}$ exposure and C-reactive protein (CRP) were published since the 2009 PM ISA. CRP is an acute phase reactant, a well-known biomarker of inflammation and clinical tool that can be used to inform decisions regarding treatment of patients with an intermediate risk of atherosclerotic cardiovascular disease (Goff et al., 2014; Pearson et al., 2003). Findings from several recent studies that considered the temporality of the $PM_{2.5}$-CRP association generally found positive associations between one- to twelve-month mean $PM_{2.5}$ exposures and log-transformed CRP as

determined by a variety of methods. These longitudinal studies leveraged the availability of repeated, time-varying measures of both the exposure and outcome, applying multi-variable adjusted mixed models and were conducted in well characterized U.S. and European cohorts including the Study of Women's Health Across the Nation (SWAN) [12.75% change (95%CI: 5.1, 21.45)] (Ostro et al., 2014) and the HNR study [22.65% change (95%CI: 13.8, 31.65)] (Hennig et al., 2014) and [11.25% change (95% CI (1.25,21.88)] (Viehmann et al., 2015). Viehmann et al. (2015) also reported results indicating that white cell count (WCC) may increase with long-term exposure to $PM_{2.5}$ [3.13% change WCC 95%CI: 0.83, 5.42)] among the HNR study population. The longitudinal analysis of the MESA cohort provided little support for an association with CRP [1% change (95%CI: -4, 6)], although a 6% (95%CI: 2, 9) higher IL-6, another indicator of systemic inflammation, was reported (Hajat et al., 2015). A meta-analysis of cross-sectional results from the ESCAPE cohorts (Lanki et al., 2015) provides little support for an association between long-term exposure to $PM_{2.5}$ and CRP [2.4% difference (95%CI: -7.5, 13.4)]. A cross-sectional analysis of the NHANES participants reported small magnitude associations of annual average $PM_{2.5}$ exposure, with CRP which was stronger in people with diabetes (Dabass et al., 2016b).

6.2.12.2 Toxicology Studies

The 2009 PM ISA included findings from several studies that pointed to inflammation in response to long-term $PM_{2.5}$ exposure, particularly in association with atherosclerotic progression (2009 PM ISA). More recent animal toxicological studies continue to provide evidence that long-term exposure to $PM_{2.5}$ may result in inflammatory effects. More specifically, a recent study demonstrated statistically significant ($p < 0.05$) changes in circulating T-cell populations in mice following long-term $PM_{2.5}$ exposure (Deiuliis et al., 2012). Similarly, in mice Kampfrath et al. (2011) demonstrated that long-term exposure to $PM_{2.5}$ results in increased ($p < 0.05$) inflammatory monocytes in the blood from the bone marrow, and that this increase in monocytes is at least partially dependent on TLR4 expression.

When examining cytokines and other inflammatory mediators, Tanwar et al. (2017) reported increased mRNA expression of the cytokines IL-1β and IL-6, as well as the matrix metalloproteinases MMP-9 and MMP-13 at birth in heart tissue of mice exposed to $PM_{2.5}$ in utero. In addition, Aztatzi-Aguilar et al. (2015) found increased ($p < 0.05$) IL-6 protein levels in mouse hearts, and Ying et al. (2013) reported increased ($p < 0.05$) Il-6, TNFα, and MCP-1 mRNA, but not e selectin, ICAM-1 or VCAM-1 in mesenteric arteries when compared to control mice exposed to FA. Similarly, an additional study in mice reported that long-term exposure to $PM_{2.5}$ was found to statistically significantly increase ($p < 0.05$) plasma levels of TNF-α and MCP-1, but not IL-6, IL 12 or Il-10, or IFN-γ when compared to control animals (Kampfrath et al., 2011). Moreover, Kampfrath et al. (2011) also demonstrated upregulation of these cytokines was at least partially dependent on TLR4 expression. In $ApoE^{-/-}$ mice, Lippmann et al. (2013a) reported increased IL-10 ($p < 0.05$) following 3 months of exposure in Manhattan, NY and decreased ($p < 0.05$) IL-6 and IL-10 at 6 months in Irvine, CA relative to control mice. Other locations did not have statistically significant changes in IL-6 or IL-10 and no location

reported appreciable changes in CRP, TNF-α, IL-13, MCP-1 or Il-12. In addition, in Irvine, CA was there a statistically significant change (increase; $p > 0.05$) in GM-CSF. Taken together, these studies may appear somewhat inconsistent, however it should be noted that markers of systemic inflammation are often transiently expressed, thus making it difficult to consistently report changes across studies that use different study designs and a variety of methodological approaches. Thus, it can be concluded that the animal toxicological evidence presented above supports long-term exposure to $PM_{2.5}$ resulting in increased markers of systemic inflammation. Moreover, there is also evidence to support that the location from which the $PM_{2.5}$ is collected influences the inflammatory response.

With respect to oxidative stress, Rao et al. (2014) reported that relative to FA, long-term exposure of $ApoE^{-/-}$ mice to $PM_{2.5}$ in resulted in increased oxidation of cholesterol. Moreover, Kampfrath et al. (2011) demonstrated that long-term exposure to $PM_{2.5}$ in mice results in an increase in NADPH oxidase derived O_2- production in the aorta. In contrast, Ying et al. (2013) did not find that long-term $PM_{2.5}$ exposure resulted in a statistically significant effect on the oxidative stress marker 8-isoprostane. Thus, there is limited evidence of oxidative stress following long-term $PM_{2.5}$ exposure. More information on studies published since the 2009 ISA can be found in Table 6-49 below.

Table 6-49 Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and inflammation and oxidative stress.

Study	Study Population	Exposure Details	Endpoints Examined
(Tanwar et al., 2017)	FVB mice, pregnant F, and offspring	In utero inhalation of 73.61 μg/m^3 $PM_{2.5}$ CAPs for 6h/day, 7 days/week throughout pregnancy.	Markers of inflammation in hearts of mice at birth after exposure in utero
(Lippmann et al., 2013a) NPACT Study 1	$ApoE^{-/-}$ mice, M, n = 4-8 per treatment group,	CAPs from Irvine, CA; Tuxedo, NY; Manhattan, NY, Lansing, MI; or Seattle, WA (138, 136, 123, 68, or 60 μg/m^3, respectively) for 6 h/day, 5 days/week for 6 mo	Markers of inflammation in blood at 3 and 6 mo post-exposure
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per treatment group	Inhalation of 178 μg/m^3 $PM_{2.5}$ from a high traffic and industrial area north of Mexico City in early summer for 5 h/day for 8 weeks (4 days/week).	Markers of inflammation in heart tissue collected 24 h post-exposure
(Ying et al., 2013)	Adult $ApoE^{-/-}$ mice, M	Inhalation of 69.6 μg/m^3 $PM_{2.5}$ CAPs for 6 h/day, 5 days/week for 12 week.	Markers of systemic inflammation in mesenteric artery tissue Marker of oxidative stress

Table 6-49 (Continued): Study-specific details from toxicological studies of long-term $PM_{2.5}$ exposure and inflammation and oxidative stress.

Study	Study Population	Exposure Details	Endpoints Examined
(Kampfrath et al., 2011)	Balb/c mice, M TLR4 null mice, M TRR4 wt mice, M	Inhalation of 92.4 μg/m^3 $PM_{2.5}$ for 6 h/day 5days/week for 20 weeks from Columbus, OH	Monocyte population counts and egress from bone marrow to blood post exposure Markers of systemic inflammation post exposure Markers of oxidative stress
(Rao et al., 2014)	ApoE$^{-/-}$ mice, M	9.1 ± 7.3 μg/m^3 from Columbus, OH fro 6 mo	Cholesterol oxidation
(Deiuliis et al., 2012)	C57BL/6 mice, M,	Inhalation of 115.5 μg/m^3 $PM_{2.5}$ for 6 h/day 5days/week for 24- 28 weeks	Changes in circulating T-cell populations post exposure

n = number, h = hour, d = day, week = week, M = male, f = female, SH = spontaneously hypertensive, CAP = concentrated ambient particle, TLR = toll like receptor

1

6.2.13 Coagulation

2 Systemic inflammation is associated with pro-coagulation effects. Fibrinogen, a soluble
3 glycoprotein and acute phase reactant that can be proteolytically converted to fibrin, cross-linked into
4 clots, and degraded into dimerized fragments called D-dimers, are potential predictors of cardiovascular
5 thrombosis. There were no studies of long-term exposure to $PM_{2.5}$ and markers of coagulation in the 2009
6 PM ISA (U.S. EPA, 2009). Several recent epidemiologic studies provide evidence that long-term
7 exposure to $PM_{2.5}$ can affect fibrinogen, D-dimer and platelet count.

6.2.13.1 Epidemiologic Studies

8 Longitudinal analyses of the U.S. or European cohorts are available. Viehmann et al. (2015)
9 reported a positive association between $PM_{2.5}$ and fibrinogen among the HNR study population [0.21%
10 change (95% CI: -2.08, 2.29)] and a positive, $PM_{2.5}$- platelet count association [4.79% change (95%CI:
11 2.92, 6.88)]. Hajat et al. (2015) observed a positive $PM_{2.5}$-D-dimer association [7% change (95% CI: 2,
12 13)] and inverse $PM_{2.5}$-fibrinogen association [-3.45 % change (-7.43, 0.52)] among MESA participants.
13 In addition, 28-day $PM_{2.5}$ was not associated with increased fibrinogen in a longitudinal analysis of the
14 NAS cohort (Bind et al., 2012). Cross-sectional studies do not generally support an association. A meta-
15 analyses of cross-sectional, study-specific results, from the ESCAPE cohorts does not indicate an
16 association between $PM_{2.5}$ and fibrinogen [0.5% change (95%CI: -1.1, 2)] (Lanki et al., 2015). A cross-
17 sectional analysis of the NHANES participants reported no association of annual average exposure to
18 $PM_{2.5}$ with fibrinogen (Dabass et al., 2016b).

6.2.14 Impaired Vascular Function and Arterial Stiffness

Endothelial dysfunction is the physiological impairment of the inner lining of the blood vessels. Endothelial dysfunction is typically measured by flow mediated dilation percent (FMD%). This method is a noninvasive technique involving measurement of the percent change in brachial artery diameter (BAD) after reactive hyperemia (increased blood flow following removal of an artery-occluding blood pressure cuff) (Thijssen et al., 2011). Biomarkers of endothelial activation, including intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), and E-selectin, soluble forms of which are released in response to inflammation-induced endothelium damage, are also examined in epidemiologic studies.

Arterial stiffness is associated with a variety of cardiovascular risk factors and outcomes (Laurent et al., 2006). Carotid-femoral pulse wave velocity (PWV) is the gold standard for directly and noninvasively measuring arterial stiffness. PWV measures the velocity at which the pulse generated by the heart travels through the arteries, typically measured by the foot-to-foot method (end diastole of the wave in the carotid artery to end diastole of the wave in the femoral artery). Increases in PWV are indicative of increased arterial stiffness. Several tools can be used to detect the pulse wave as it travels, including pressure, distension, and Doppler, allowing PWV to be calculated as the distance divided by change in time between the two points. Augmentation index is an indirect measure of arterial stiffness and cannot be used in place of PWV in assessing regional stiffness; however, its measurement in concert with PWV can provide additional evidence for arterial stiffness. Large and small artery compliance and Young's modulus (a measure of elasticity adjusted for wall thickness) are measures of local arterial stiffness, which require more advanced measurement techniques. Aside from PWV, evidence supporting the validity of arterial stiffness measures as predictors of cardiovascular outcomes is not extensive.

6.2.14.1 Epidemiologic Studies

There were no epidemiologic studies of long-term exposure to $PM_{2.5}$ and FMD, BAD or markers of endothelial activation reviewed in the 2009 PM ISA. A limited number of studies have been published subsequently. In an analysis of MESA data, Krishnan et al. (2012) reported that $PM_{2.5}$ was inversely associated with FMD% [-0.50% change FMD (95% CI: -1.00, -0.05)] with potential effect modification by sex, smoking status, age, and hypertensive status but not associated with BAD [0.00% difference BAD (95% CI: -0.10, 1.00)]. Wilker et al. (2014) reported a comparable inverse association [-0.40 % change (95% CI: -0.68, -0.13)] between $PM_{2.5}$ and FMD% among a subset of participants in the Framingham Offspring Study and Third Generation Studies. Wilker et al. (2014) also examined associations with measures of arterial and microvascular function, BAD, baseline mean flow velocity, and mean hyperemic flow velocity. Only hyperemic flow velocity was additionally associated with $PM_{2.5}$ [-1.80 % change (95%CI: -3.45, -0.15)] These effects are relatively large given that normal ranges are between 5-10% (Järhult et al., 2009). Hajat et al. (2015) observed no association of annual $PM_{2.5}$ exposure with soluble

ICAM-1 [-2.07% (95% CI: -7.69, 3.56)] or E-selectin [1.08 % (95%CI: -0.66, 2.82)]. In addition, Tallon et al. (2017) reported an association [OR: 1.27 (95%CI:0.87, 1.84)] with erectile dysfunction, which may be a consequence of $PM_{2.5}$-mediated effects on vascular function.

There were no studies of long-term $PM_{2.5}$ exposure and PWV reviewed in the 2009 PM ISA. Currently available studies do not provide evidence of an effect of $PM_{2.5}$ on arterial stiffness. A cross-sectional analysis of the Atherosclerosis Risk in Young Adults study in which PWV could only be measured in a subset of participants (Lenters et al., 2010) reported no association [−0.99 % change PWV (95% CI: -6.7, 4.71)]. Similarly, O'Neill et al. (2011) measured large and small artery compliance as well as Young's modulus among participants in the MESA population and found no associations between $PM_{2.5}$ and arterial stiffness overall or stratified by sites [0.4% difference PWV (95% CI: 0.7, -0.15)]. There was evidence of possible effect modification by race and diabetes (O'Neill et al., 2011).

6.2.14.2 Toxicology Studies

Since the publication of the 2009 PM ISA, Ying et al. (2015) reported that in SH rats, long-term exposure to $PM_{2.5}$ resulted in statistically significant ($p < 0.05$) reduced vasodilation in response to the vasodilator acetylcholine. Similarly, these authors also demonstrated that long-term exposure to $PM_{2.5}$ resulted in a statistically significant ($p < 0.05$) increase in the contractile response following treatment of aortic rings with vasoconstrictors. Thus, long-term $PM_{2.5}$ exposure can result in greater contractility and reduced dilation in SH rats. These results are in agreement with an additional study in mouse aortic rings that reported both reduced vasodilation in response to acetylcholine as well as increased contractile response following vasoconstrictor treatment (Kampfrath et al., 2011). Thus there is some evidence that long-term exposure to $PM_{2.5}$ can result in impaired vascular function. More information on these studies can be found in Table 6-50 below.

Table 6-50 Study specific details from toxicological studies of long-term $PM_{2.5}$ exposure and impaired vascular function.

Study	Study Population	Exposure Details	Endpoints Examined
(Ying et al., 2015)	4 week old SH rats, M, n = 6/treatment group	Inhalation of 128.3 ± 60.4 $\mu g/m^3$ $PM_{2.5}$ CAPs Exposed 6 h/day, 5 days/week for 15 week from Columbus, OH	contractility of rat aortic rings, Hypertrophic markers 15 week post
(Kampfrath et al., 2011)	Balb/c mice, M TLR4 null mice, male TRR4 wt mice, male	Inhalation of 92.4 $\mu g/m^3$ $PM_{2.5}$ for 6 h/day 5 days/week for 20 weeks from Columbus, OH	contractility of mouse aortic rings

n = number, m = male, h = hour, week = week, CAP = concentrated ambient particle.

6.2.15 Copollutant Confounding

The independence of the association between long-term exposure to $PM_{2.5}$ and cardiovascular health effects can be examined through the use of copollutant models. A change in the $PM_{2.5}$ risk estimates, after adjustment for copollutants, may indicate the potential for confounding. Recent studies presenting copollutant model results address a previously identified data gap by informing the extent to which effects associated with exposure to $PM_{2.5}$ are independent of co-exposure to correlated copollutants in long-term analyses. A limited number of studies are available to assess copollutant confounding of the association between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity (Figure 6-20). Overall, risk estimates from these few studies remain largely unchanged after adjustment for $PM_{10-2.5}$, NO_2, and $PM_{2.5}$ from traffic sources.

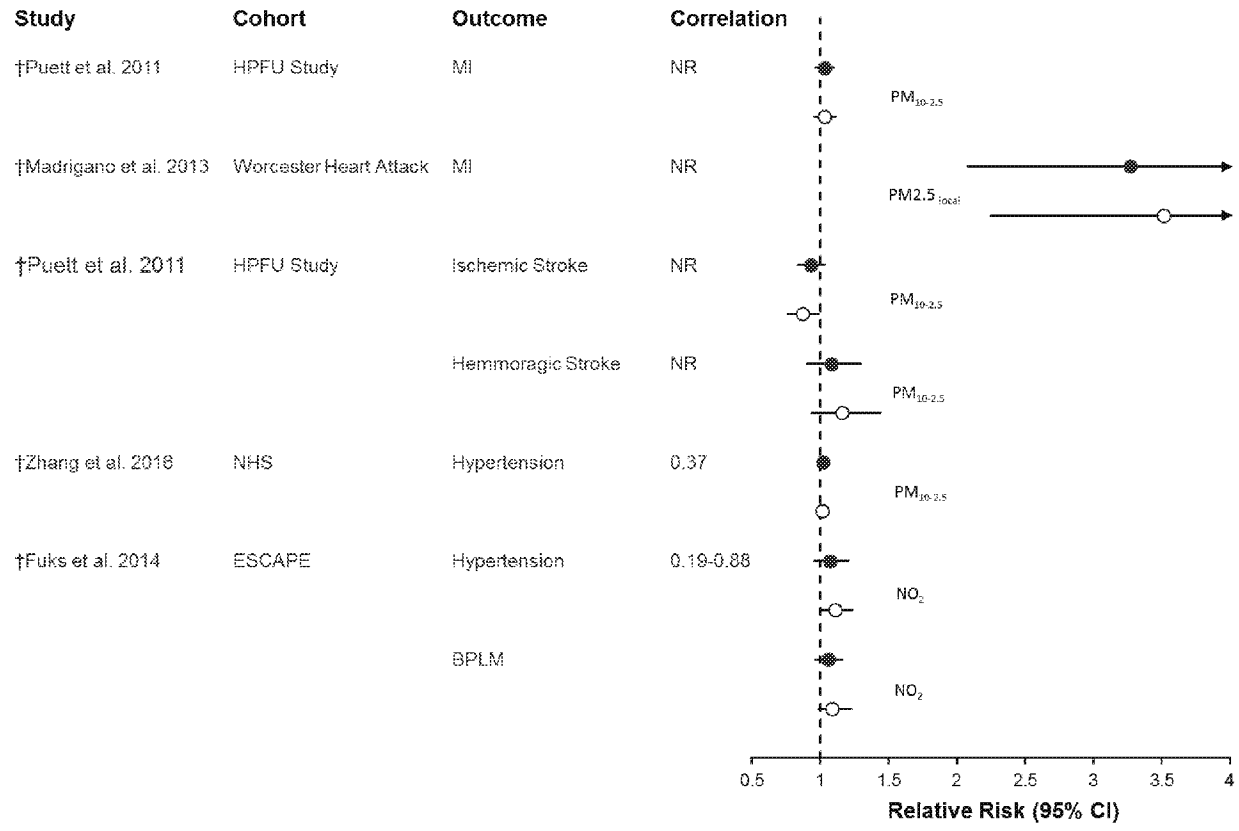
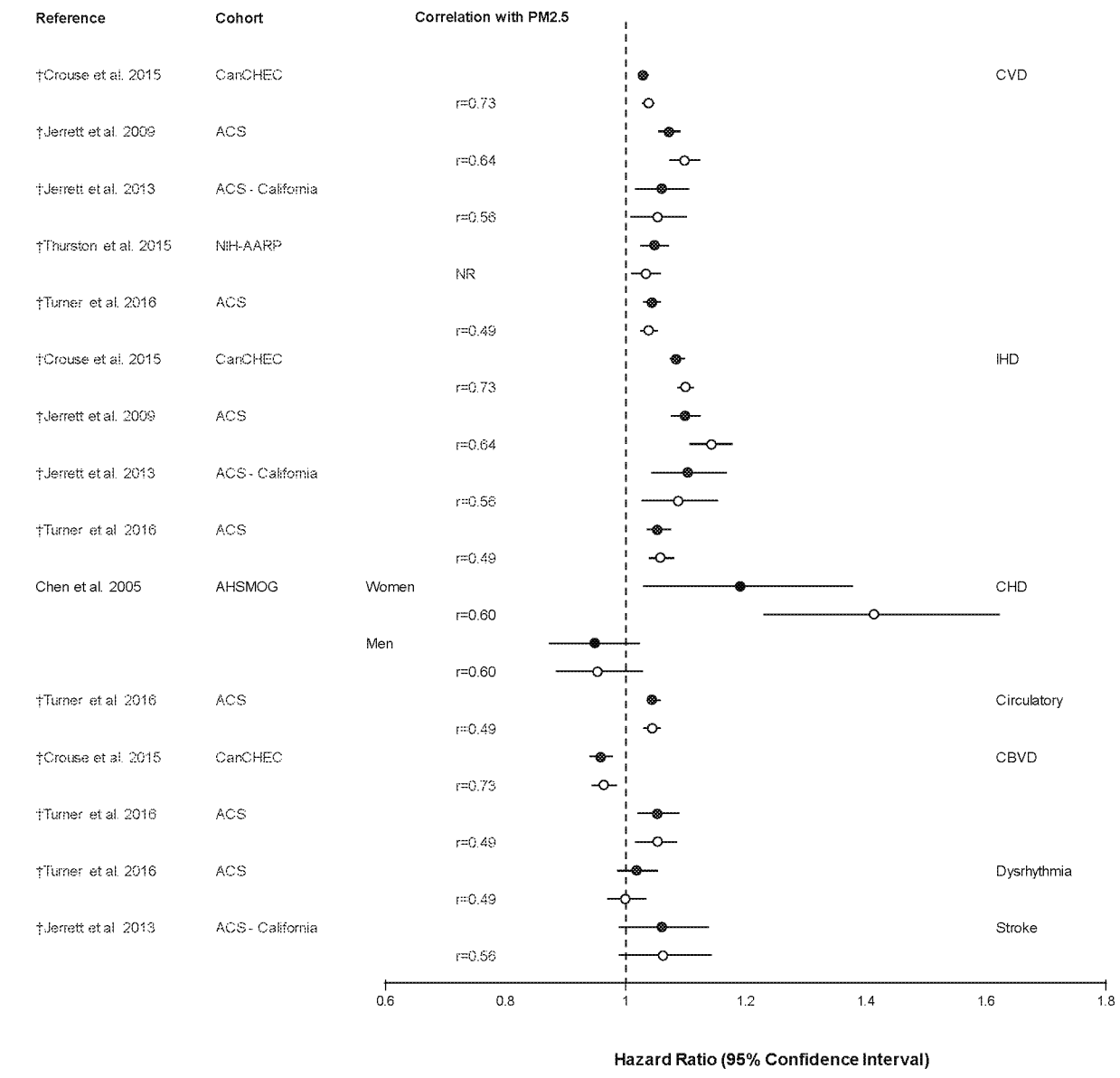


Figure 6-20 Associations between long-term exposure to $PM_{2.5}$ and cardiovascular morbidity in single pollutant models and models adjusted for copollutants.

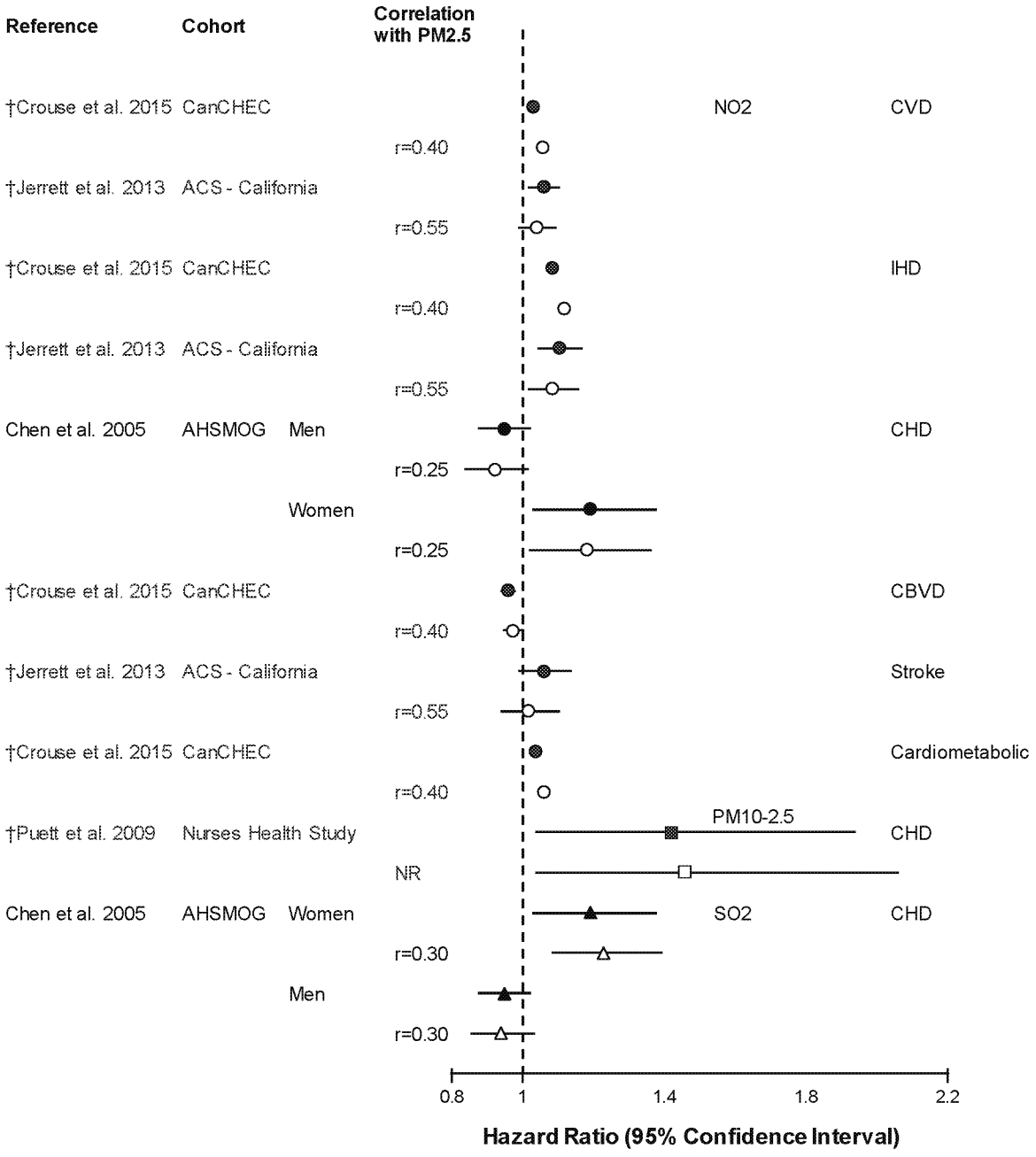
There is a larger body of studies that examined the potential for copollutant confounding of the association between long-term exposure to $PM_{2.5}$ and mortality from cardiovascular causes. The results for associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality in single pollutant models and copollutant models adjusted for ozone are shown in Figure 6-21. The correlations between $PM_{2.5}$ and ozone exposures in the studies that conducted copollutant analyses were generally positive and moderate to strong, ranging from $r = 0.49$ to 0.73. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for ozone. The trend persisted across different specific causes of cardiovascular mortality. There was one exception to the trend. The effect of long-term $PM_{2.5}$ exposure on CHD mortality among women in the AHSMOG cohort (Chen et al., 2005) increased after adjusting for ozone in the model. The results for associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality in single pollutant models and copollutant models adjusted for NO_2, $PM_{10-2.5}$, or

SO_2 are shown in Figure 6-22. The correlations between $PM_{2.5}$ and NO_2 exposures in studies that conducted copollutant analyses were positive and weak ($r = 0.25$) or moderate ($r = 0.40$; $r = 0.55$). The correlations between $PM_{2.5}$ and $PM_{10-2.5}$ were not reported in the single study evaluating coarse particles (Puett et al., 2009). One study evaluated SO_2 (Chen et al., 2005) in copollutant models and reported a correlation of $r = 0.30$. Generally, the $PM_{2.5}$ effect estimates remained relatively unchanged in copollutant models adjusted for NO_2, $PM_{10-2.5}$, or SO_2.



Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles represent point estimates, horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Black circles represent effect of $PM_{2.5}$ in single pollutant models, white circles represent effect of $PM_{2.5}$ adjusted for ozone. ACS: American Cancer Society Cohort; CanCHEC = Canadian Census Health and Environment Cohort; NIH-AARP: National Institutes of Health American Association of Retired Persons Diet & Health Cohort; AHSMOG: Adventist Health Air Pollution Study; CVD: cardiovascular; IHD: ischemic heart disease; CHD: coronary heart disease; CBVD: cerebrovascular disease; CPD: cardiopulmonary disease; COPD: chronic obstructive pulmonary disease; NR: not reported. †Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Figure 6-21 Associations between long-term exposure to $PM_{2.5}$ and cardiovascular mortality in single pollutant models and models adjusted for ozone.



Associations are presented per 5 μg/m^3 increase in pollutant concentration. Circles, squares, and triangles represent point estimates, horizontal lines represent 95% confidence intervals for $PM_{2.5}$. Filled symbols represent effect of $PM_{2.5}$ in single pollutant models, open circles represent effect of $PM_{2.5}$ adjusted for NO_2; open squares represent effect of $PM_{2.5}$ adjusted for $PM_{10-2.5}$; open triangles represent effect of $PM_{2.5}$ adjusted for SO_2. ACS: American Cancer Society Cohort; AHSMOG: Adventist Health Air Pollution Study; CanCHEC = Canadian Census Health and Environment Cohort; CVD: cardiovascular; IHD: ischemic heart disease; CHD: coronary heart disease; CBVD: cerebrovascular disease; NR: not reported. †Studies published since the 2009 Integrated Science Assessment for Particulate Matter.

Figure 6-22 Long-term exposure to $PM_{2.5}$ and cardiovascular mortality in single pollutant models and models adjusted for other pollutants.

6.2.16 Shape of the Concentration-Response Function

An important consideration in characterizing the association between long-term $PM_{2.5}$ exposure and mortality is whether the concentration-response relationship is linear across the full concentration range that is encountered, or if there are concentration ranges where there are departures from linearity. The 2009 PM ISA characterized the results of an analysis by Miller et al. (2007) that demonstrated that the shape of the concentration-response curve for cardiovascular mortality was generally linear. Recent studies add to the evidence base on the C-*R* relationships for cardiovascular morbidity (Table 6-51) and mortality (Table 6-52) outcomes. However, complicating the interpretation of these results is both the lack of thorough empirical evaluations of alternatives to linearity as well as the results from cut-point analyses that provide some potential indication for nonlinearity in the relationship between long-term $PM_{2.5}$ exposure and cardiovascular disease.

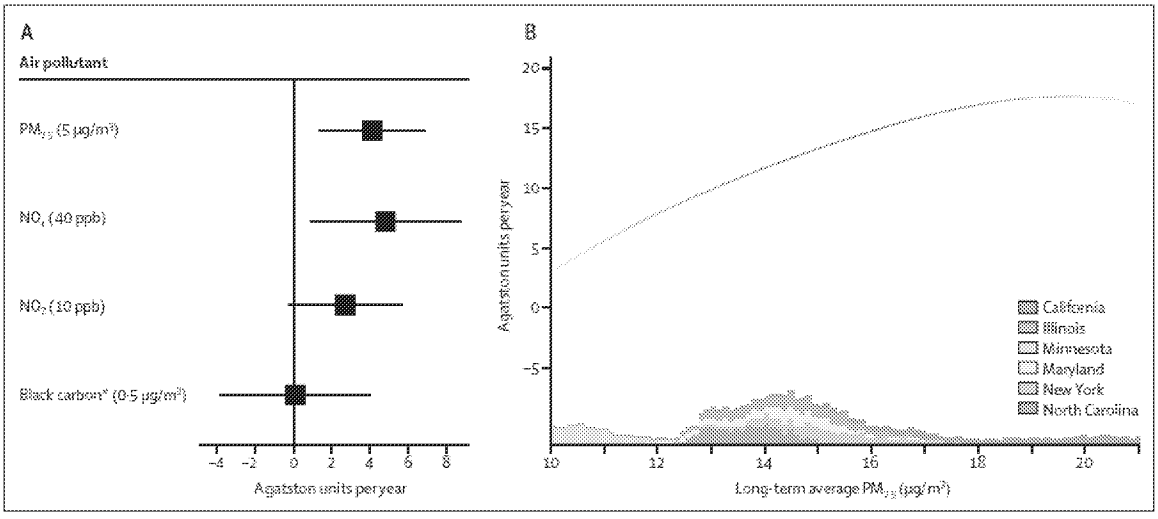
Two analyses of the C-*R* function for the relationship between $PM_{2.5}$ and CAC are available. Kaufman et al. (2016) generated a C-*R* curve using a thin plate regression spline with 5 degrees of freedom. The curve shows an increase in CAC with increasing long-term exposure to $PM_{2.5}$ and attenuation of the curve at higher concentrations (Figure 6-23). Dorans et al. (2016) reported a deviation from linearity such that log transformed CAC increased with increasing $PM_{2.5}$ concentrations at lower concentrations (<~10μg/m^3) while log transformed CAC decreased with increasing $PM_{2.5}$ at higher concentrations (Figure 6-24). A restricted cubic spline with 5 knots was used to examine the shape curve. The concentration and variability in the $PM_{2.5}$ concentrations were notably lower in the Framingham Heart Study cohort compared to the MESA population.

Chen et al. (2014a) examined the shape of the C-*R* function or the relationship between long-term $PM_{2.5}$ exposure and hypertension using a natural cubic spline with 2 degrees of freedom, is shown in Figure 6-25. The reference concentration for the HRs, which generally increase in a linear fashion, was 2.9 μg/m^3. In an analysis of IHD incidence, Cesaroni et al. (2014) restricted the data used in their meta-analysis of ESCAPE cohorts to include only those exposed below various thresholds. For the cohorts with participants exposed to <15 μg/m^3 average annual $PM_{2.5}$, the meta-analyzed HR for the association of long-term $PM_{2.5}$ exposure and IHD incidence was like the HR for the entire range of concentrations [1.19 (95%CI: 1.00, 1.42)].

Table 6-51 Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and cardiovascular morbidity.

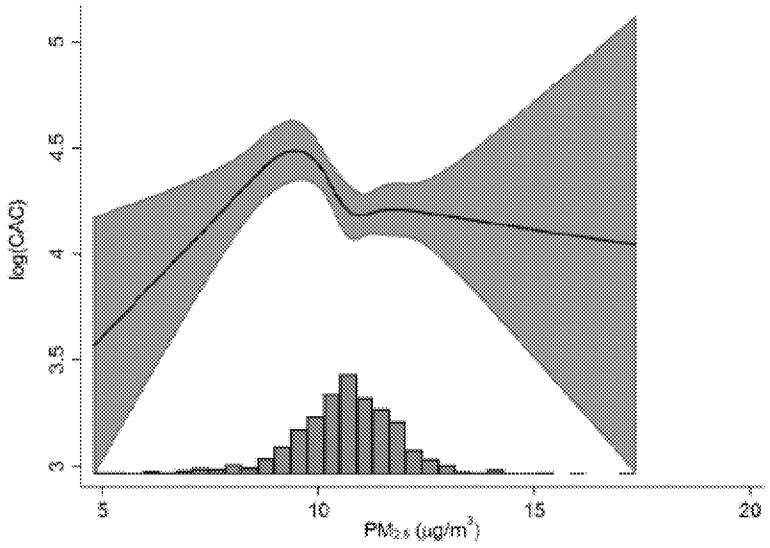
Study Location – Cohort (Table/Figure from Reference)	Outcome	Exposure $PM_{2.5}$ Mean: (Range) in $\mu g/m^3$	Statistical Analysis Summary
Cesaroni et al. (2014) 11 Cohorts Europe ESCAPE	IHD Incidence	NR	Restricted the meta-analysis to persons exposed below various thresholds. HR <15 $\mu g/m^3$ similar to HR across the full range of concentrations
Kaufman et al. (2016) 6 Urban sites U.S. MESA	CAC	Mean: 14.2 (range: 9.2-22.6)	Thin plate regression spline with 5 degrees of freedom. Attenuation at higher concentrations suggested
Dorans et al. (2016) Framingham Heart Study Offspring	CAC	Median (IQR) = 10.7 (1.4) for 2003	Restricted cubic spline with 5 knots. Non-linear relationship of log CAC with long-term $PM_{2.5}$ concentration observed
Chen et al. (2014a) Ontario, Canada	Hypertension	Mean 10.7 (range 2.9-19.2)	Natural cubic spline with 2 degrees of freedom (reference concentration 2.9 $\mu g/m^3$). No evidence of departure from linearity across the range of concentrations

CAC = coronary artery calcium, ESCAPE = European Study of Cohorts for Air Pollution Effects, HR = hazard ration, IHD = ischemic heart disease, IQR = interquartile range.



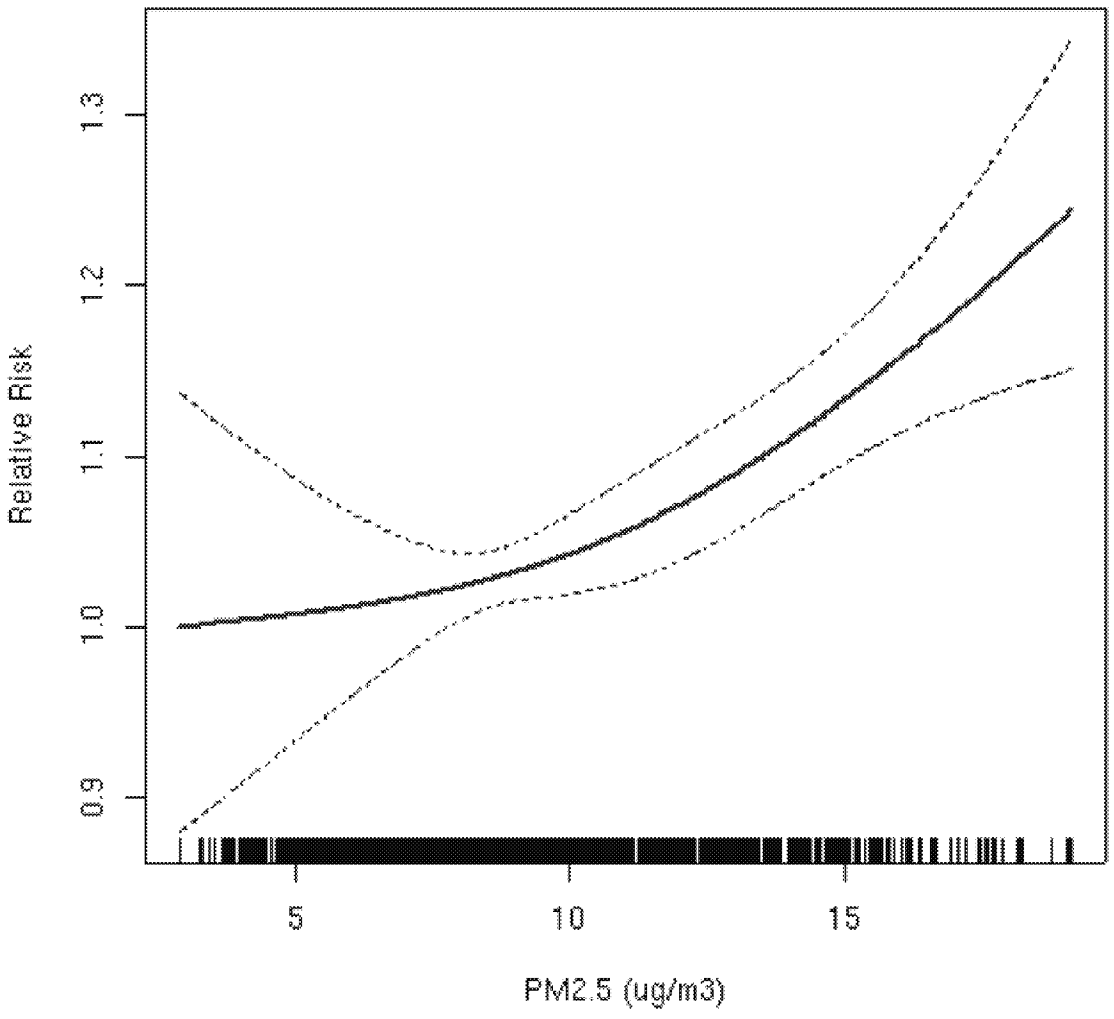
Source: Permission pending, (Kaufman et al., 2016)

Figure 6-23 The linear longitudinal association of long-term average $PM_{2.5}$ concentrations with coronary artery calcification (CAC) progression (Agatston units per year) across the range of concentrations.



Source: Permission pending, (Dorans et al., 2016)

Figure 6-24 Non-linear association of annual average $PM_{2.5}$ concentration (2003) and natural log-transformed coronary artery calcification (CAC).



Source: Permission pending, (Chen et al., 2014a)

Figure 6-25 Concentration-response relationship between the concentration of $PM_{2.5}$ and incident hypertension. The relative risks are adjusted covariates including sex, marital status, education, income body mass index (BMI), physical activity, smoking alcohol, diet race, urban residency neighborhood level socioeconomic status (SES) and unemployment rate, diabetes and COPD.

A number of recent studies have conducted analyses to inform the shape of the concentration-response relationship for the association between long-term exposure to $PM_{2.5}$ and mortality, and are summarized in Table 6-52. Generally, the majority of the results from these analyses continue to support a

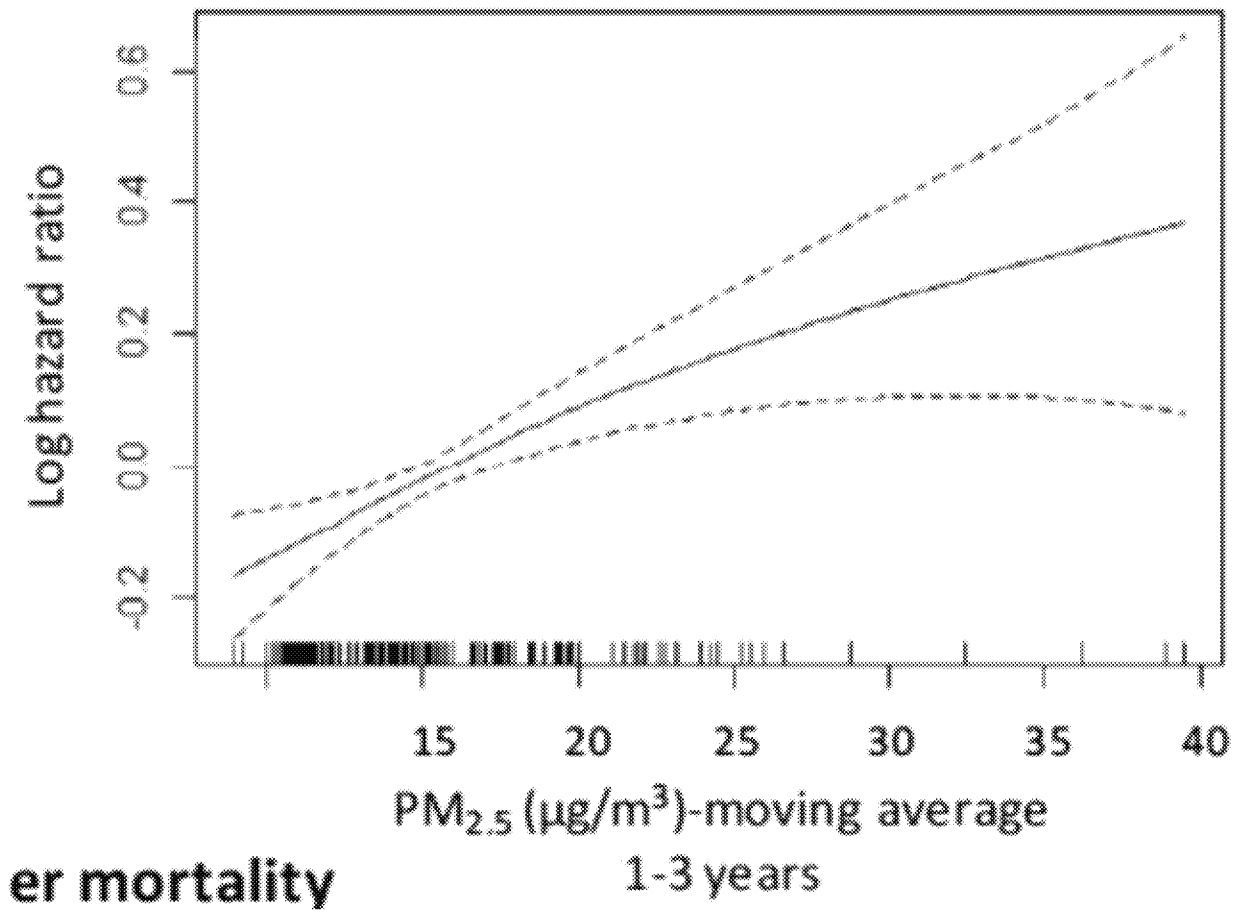
linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of $PM_{2.5}$. A number of the concentration-response analyses include concentration ranges ≤12 μg/m^3. For example, Lepeule et al. (2012) observed a linear, no-threshold concentration-response relationship for cardiovascular mortality in the most recent analysis of the Harvard Six Cities study, with confidence in the relationship down to a concentration of 8 μg/m^3 (Figure 6-26). Similar linear, no-threshold concentration-response curves were observed for cardiovascular mortality in other studies (Thurston et al., 2015; Villeneuve et al., 2015; Cesaroni et al., 2013; Gan et al., 2011). However, some studies reported that the slope of the concentration-response function tended to be steeper at lower concentrations, especially for IHD mortality. For example, in Crouse et al. (2012) statistical tests did not provide evidence for departure from linearity in the concentration-response function for IHD, but the risk was greater (HR = 1.20) at lower concentrations (<10 μg/m^3) compared to higher concentrations (10-15 μg/m^3) of $PM_{2.5}$ (Figure 6-27). Similar results were observed in other studies (Jerrett et al., 2016; Weichenthal et al., 2014b). Additional evidence to support a supralinear concentration-response relationship comes from a series of studies that looked at exposure to $PM_{2.5}$ from both ambient air pollution and cigarette smoke (Pope et al., 2011; Pope et al., 2009). These studies concluded that including the full concentration range of $PM_{2.5}$ from both ambient air pollution and cigarette smoking, it is clear that the relationship between long-term exposure and cardiovascular mortality cannot be adequately characterized as linear with no threshold. The concentration-response relationship is much steeper at lower $PM_{2.5}$ concentrations (such as those due to ambient air pollution) compared to the higher concentrations associated with cigarette smoking. This indicates the importance of considering the cause of death when characterizing the concentration-response relationship between long-term $PM_{2.5}$ exposure and cardiovascular mortality.

Table 6-52 Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and cardiovascular mortality.

Study Location – Cohort (Table or Figure from Reference)	Exposure $PM_{2.5}$ Mean; (Range) in μg/m^3	Statistical Analysis Summary
Cesaroni et al. (2013)	Eulerian Dispersion Model (1 km x 1 km)	Natural splines with 2, 3, or 4 df, compared goodness of fit using BIC and likelihood ratio test
Italy–RoLS	23.0; (7.2-32.1)	No evidence of deviation from linearity; Results similar for 2, 3 or 4 df
(Figure 2B)		

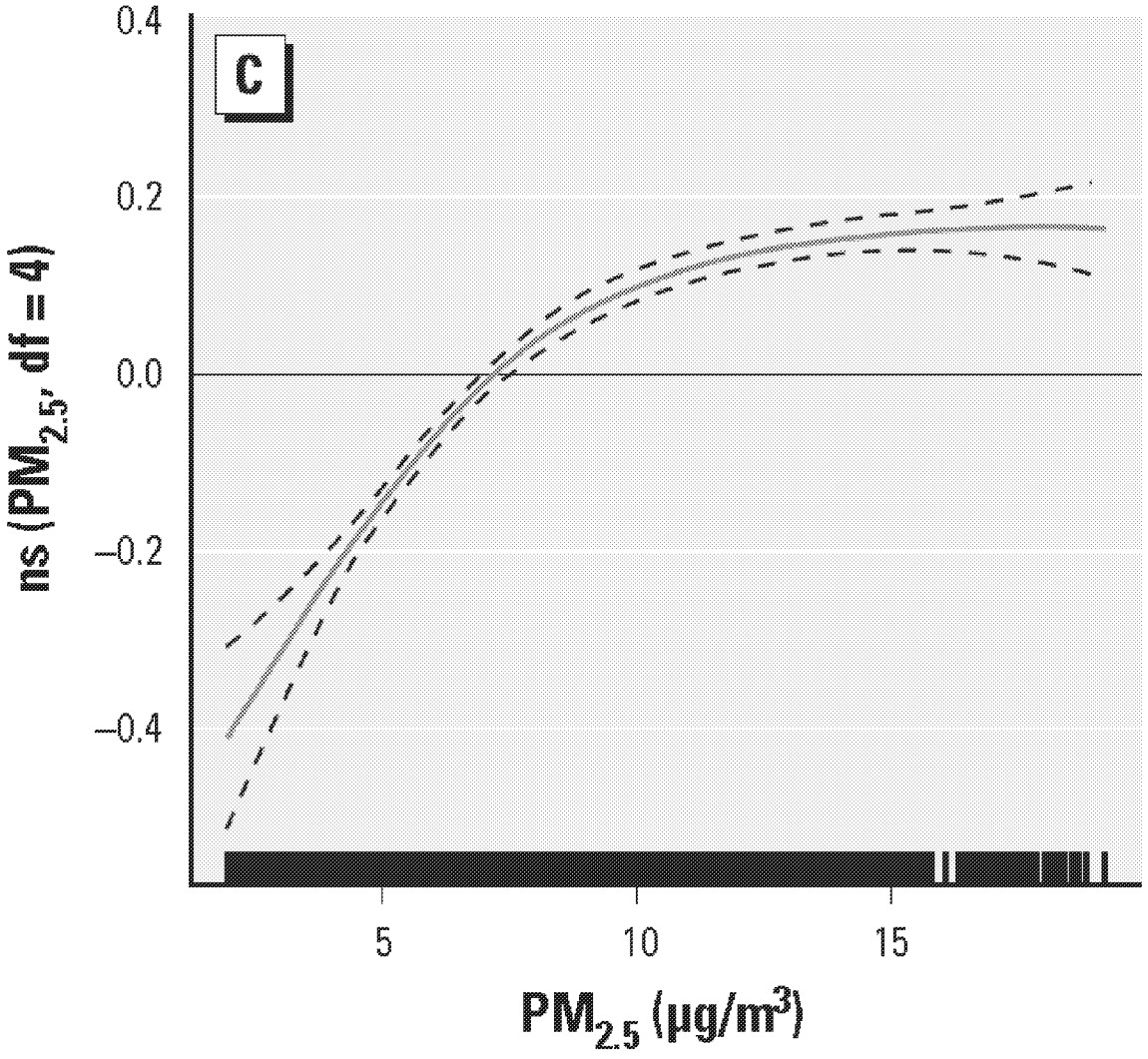
Table 6-52 (Continued): Summary of studies examining the concentration-response relationship or conduction threshold analyses for long-term exposure to $PM_{2.5}$ and cardiovascular mortality.

Study Location – Cohort (Table or Figure from Reference)	Exposure $PM_{2.5}$ Mean; (Range) in $\mu g/m^3$	Statistical Analysis Summary
Crouse et al. (2012) Canada – CanCHEC (Figure 2A-D)	Ground monitors in 11 cities; Satellite RS (10 km x 10 km) 11.2; (1.9-19.2)	Natural splines with 2, 3, or 4 df, compared goodness of fit using BIC. Log function of $PM_{2.5}$ ($\ln[PM_{2.5} + 1]$) yielded lower BIC than each of the spline models No evidence for departure from linearity for, CVD or CBVD. Risk was higher (HR = 1.20) from 5 $\mu g/m^3$ to 10 $\mu g/m^3$, and lower (HR = 1.12) from 10 $\mu g/m^3$ to 15 $\mu g/m^3$ for IHD mortality
Gan et al. (2011) Canada – Metro Vancouver (Figure 1b)	LUR 4.08; (0-10.24)	Study subjects divided into quintiles based on $PM_{2.5}$ concentration Consistent magnitude of RRs across quintiles suggests linearity. (Magnitude of effect is near null)
Jerrett et al. (2016) U.S. – ACS (Figures S2 and S3)	BME LUR: 12.0; (1.5-26.6) Satellite RS: 11.9; (1.9–24.6)	Natural splines with 2 df BME LUR curve is generally linear and has a steeper slope compared to the satellite RS curve, though slope decreases at concentrations above 20 $\mu g/m^3$; satellite RS curve is generally linear though slope begins to flatten for concentrations above has 13 - 15 $\mu g/m^3$
Lepeule et al. (2012) U.S.–HSC (Supplemental Figure 1)	Ground Monitor 15.9; (11.4-23.6)	Penalized spline models Linear relationship with exposures down to 8 $\mu g/m^3$. No evidence of a threshold. Highest confidence from 10 – 20 $\mu g/m^3$ based on greatest data density
Thurston et al. (2015) U.S.–NIH–AARP (Figure 2)	Hybrid LUR geo-statistical model 12.2; (2.9 – 28.0)	Natural spline plots with 4 df (Referent HR = 1.0 at mean exposure level) Observed linear relationship
Villeneuve et al. (2015) Canada–CNBSS (Figure 3)	Satellite RS (10 km x 10 km) 9.1; (0.1 – 20.0)	C-*R*: Natural cubic spline functions with 3 df; Threshold analysis: newly defined exposure variables based on concentration corresponding to the largest log-likelihood value from the Cox model Linear relationships for CVD and IHD mortality; Threshold analysis demonstrates no improvement in fit over a no-threshold linear model for CVD and IHD mortality
Weichenthal et al. (2014b) U.S.–Ag Health (Figure 2)	Satellite RS (10 km x 10 km) 8.84; (5.7-19.2)	Natural splines with 2 df. Natural splines with 3 and 4 df were examined but didn't not improve model fit Linear increase observed from 6 to 10 $\mu g/m^3$, with slope flattening out for concentrations between 10 and 14 $\mu g/m^3$



Source: Reprinted with permission from (Lepeule et al., 2012)

Figure 6-26 Concentration-response relationship between long-term $PM_{2.5}$ exposure and cardiovascular mortality in the Harvard Six Cities Study using penalized splines (1974–2009).



Source: Reprinted with Permission from (Crouse et al., 2012)

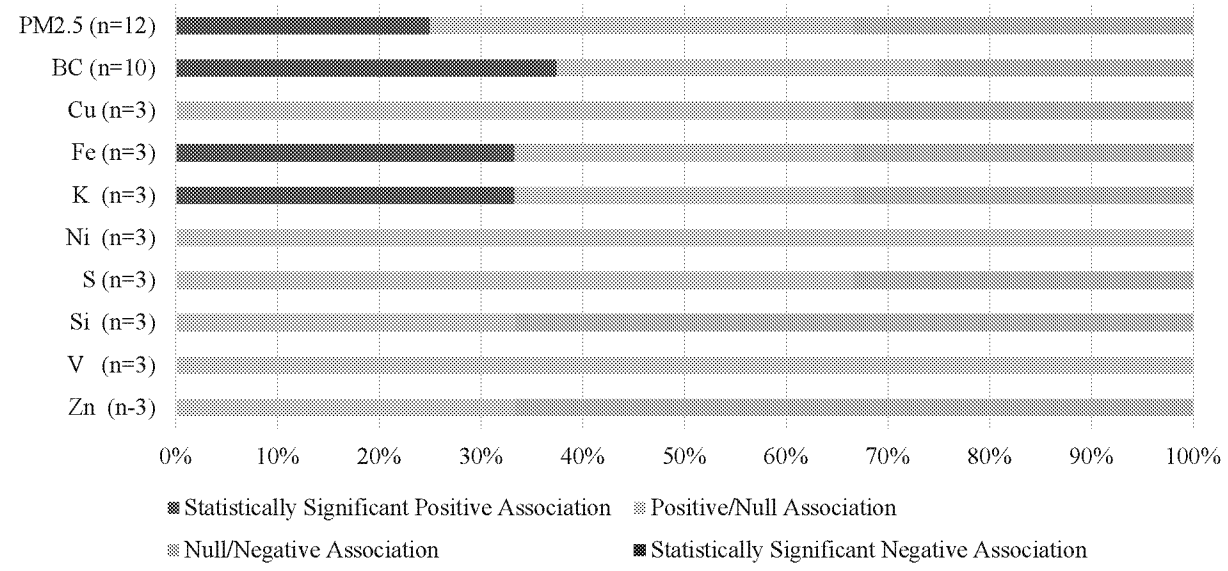
Figure 6-27 Concentration-response curve for IHD mortality in the CanCHEC cohort study. (Mean $PM_{2.5}$: 8.7 µg/m^3; natural splines with four degrees of freedom). Dotted lines indicate 95% confidence intervals.

6.2.17 Associations between $PM_{2.5}$ Components and Sources and Cardiovascular Effects

There were no studies that examined the association between $PM_{2.5}$ components and cardiovascular outcomes available for review in the 2009 PM ISA. A limited number of studies have been published since the previous review. Overall, this set of studies reports a range of findings from positive and statistically significant to null or negative (Figure 6-28). Figure 6-29 presents associations for specific

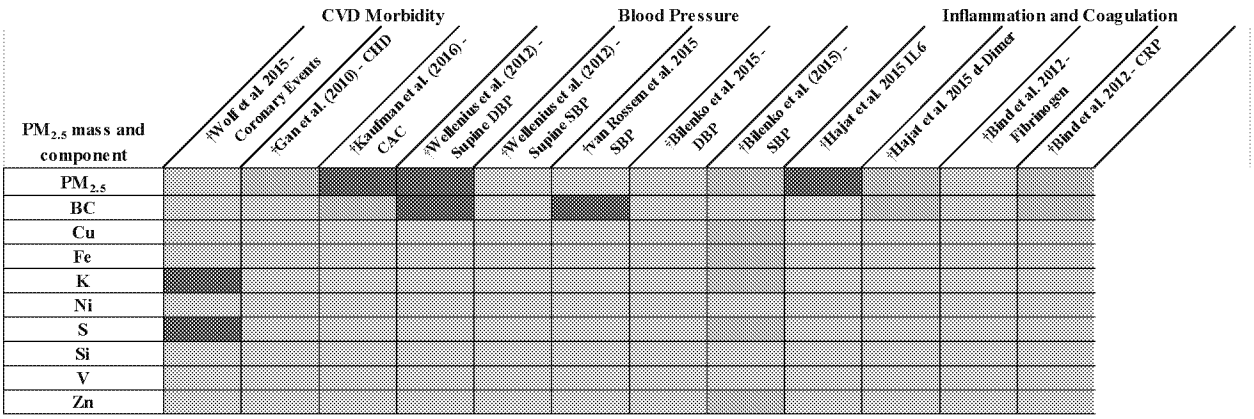
studies showing the lack of comparability across studies regarding the cardiovascular outcome and the component examined.

Wolf et al. (2015b) positive associations of $PM_{2.5}$ and $PM_{2.5}$ components with coronary events in the ESCAPE cohort. Gan et al. (2011) reported an association between long-term black carbon (BC) exposure and CHD hospitalizations but not between long-term $PM_{2.5}$ exposure and CHD hospitalizations in Vancouver, Canada. As discussed in Section 6.2.4 on atherosclerosis, Kaufman et al. (2016) reported a longitudinal association between exposure to $PM_{2.5}$ and CAC, but not between $PM_{2.5}$ and cIMT as indicated in the interim analysis of Adar et al. (2013). Consequently, associations of $PM_{2.5}$ components with cIMT (Kim et al., 2014; Sun et al., 2013) are not pictured in Figure 6-28. Kaufman et al. (2016) did not observe an association between black carbon (BC) and increased CAC. Wellenius et al. (2012b) reported significant associations of both 28-day average $PM_{2.5}$ and 28-day average BC exposure with resting supine DBP. Non-significant increases between both pollutants and resting supine SBP were also observed. Association between $PM_{2.5}$ and most measured components and DBP were observed among children (12 years old) participating in the PIAMA cohort in the Netherlands (Bilenko et al., 2015a). Positive associations between IL-6 and fibrinogen but not CRP or d-Dimer were observed for both $PM_{2.5}$ and BC (Hajat et al., 2015; Bind et al., 2012).



Note: Bars represent the percent of associations across studies for $PM_{2.5}$ mass or $PM_{2.5}$ components for long-term exposure studies of cardiovascular outcomes where dark blue = statistically significantly positive, light blue = positive/null, light orange = null/negative, red = statistically significantly negative N = number of studies that provided an estimate. $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 µm, BC = black carbon, Cu = copper, Fe = iron, K = potassium, Ni = nickel, S = sulfur, Si = silica, V = vanadium, Zn = zinc

Figure 6-28 Distribution of associations of long-term exposure to $PM_{2.5}$ and $PM_{2.5}$ component concentrations with cardiovascular outcomes.



Note: Cells represent associations examined for studies of long-term exposure to $PM_{2.5}$ mass and $PM_{2.5}$ components and cardiovascular outcomes. Dark blue = statistically significant positive association; light blue = positive or null association; light orange = null or negative association; red = statistically significant negative association; grey = component not examined. Only $PM_{2.5}$ components for which there were at least three studies available were included in the table. $PM_{2.5}$ = particulate matter with mean aerodynamic diameter 2.5 μm, BC = black carbon, Cu = copper, Fe = iron, K = potassium, Ni = nickel, S = sulfur, Si = silica, V = vanadium, Zn = zinc.

Figure 6-29 Results of studies of long-term exposure to $PM_{2.5}$ and $PM_{2.5}$ component concentrations and cardiovascular outcomes.

Regional Heterogeneity

The 2009 PM ISA concluded that there is variation in both $PM_{2.5}$ mass and composition between cities and that the variation may be due, in part to differences in $PM_{2.5}$ sources as well as meteorology and topography. Although east-west gradients were observed for PM components including SO_4^{2-}, OC, and NO_3^-, the amount of city-specific speciated $PM_{2.5}$ data was limited and did not explain the heterogeneous effect estimates for PM across locations. There were no national-scale studies that examined regional differences in the associations between long-term exposure to $PM_{2.5}$ and cardiovascular effects included in the 2009 PM ISA, however, a large U.S.-based multicity study of short-term exposure and CVD hospital admissions provided evidence indicating larger risks in the Northeast compared to the West and multicity epidemiologic studies of cardiovascular mortality generally observed a similar pattern.

A limited number of studies published since the 2009 PM ISA examine regional differences in the associations between long-term exposure and cardiovascular outcomes including CHD and stroke. An analysis of region specific HRs in the NHS indicated slight increases in the Northeast and the South compared to the Midwest and West, although confidence intervals were wide. In a sensitivity analyses restricted to more recent years (2000-2006) the regional differences were more pronounced. Note that Hart et al. (2015b) observed no of association between long-term exposure to $PM_{2.5}$ and incident CHD [HR: 1.01 95%CI: 0.96,1.07], overall. Feng and Yang (2012) compared prevalence odds ratios across nine U.S. regions reporting that the largest ORs for the associations with MI and CHD were in "east central" region of the US.

Sources

The literature examining the relationship between sources of $PM_{2.5}$ and health effects that was included in the 2009 PM ISA was limited to a small number of studies examining the associations of traffic-related sources with mortality. The evidence provided by these studies was not sufficient to distinguish specific sources that could be linked to health effects. The currently available studies on this topic are tabulated below. Aguilera et al. (2016) reported an association between cIMT and $PM_{2.5}$ from traffic but not between cIMT and $PM_{2.5}$ from crustal sources. Positive cross-sectional associations of cIMT with traffic load and traffic intensity were reported in a meta-analysis of four ESCAPE cohorts. $PM_{2.5}$ from traffic exhaust was associated with readmission for MI in MINAP study in London (Tonne et al., 2015). Overall, these studies were not designed to evaluate whether long-term exposure to $PM_{2.5}$ traffic sources was more strongly or independently associated with cardiovascular health effects, however.

6.2.17.1 Toxicology Studies of Individual Components and Sources as Part of a PM Mixture

Campen et al. (2014) exposed young, male $ApoE^{-/-}$ mice on a high fat, high cholesterol diet to motor vehicle exhaust (MVE), MVE with particles removed, sulfate particles, ammonium nitrate particles or paved road dust at target concentrations of 300 $\mu g/m^3$ for 50 days (6 hr/day, 7 day/week). Given that the MVE exposures included gases, the focus of the discussion on this study is on those exposures that contained particles only. Measurements informative for biologic pathways of vascular toxicity, atherosclerosis, and coronary artery disease were obtained the day following the last exposure. Multiple Additive Regression Tree (MART) analysis was performed to assess the relationship between concentrations of individual components with the measurements of biological endpoints. Ultimately a "predictor values" of ranked components is produced based on the strength of their association with each biological marker. In addition, an estimated concentration-response curve is generated using the biological outcome and the predictor after accounting for the average effects of all other chemical predictors across their experimental exposure ranges. MART analysis chemical predictor variables include particle mass, ammonium, elements, nitrate, sulfate, EC, OC, particle phase organics (i.e., organic acids, organic phenols, organic sterols, organic sugars, organic hopanes, organic steranes, organic PAHs, organic nitro-PAHs, and organic alkanes). There were very few changes in biologic endpoints compared to control animals exposed to air for the sulfate, ammonium nitrate or road dust exposures. The sulfate exposure did result in significant enhancement of PE-induced contraction in mouse aortas compared to air controls, with ammonium nitrate exposure resulting in significantly diminished PE-induced contraction compared to air controls. Plaque area was also increased and linked to ammonium nitrate, albeit the group size was quite small (as low as 3). Two measurements appeared dependent on PM (more so than the gases) – oxidized low-density lipoprotein and vasoconstriction. However, in general, MVE gases were

required to elicit significant responses in toxicological measurements and the PM alone did not appear to drive any of the statistically significant effects observed.

Chen et al. (2010) examined mice exposed to Manhattan and Sterling Forest (aka Tuxedo) CAPs as a part of the NPACT study. They evaluated changes in HR and HRV parameters with source categories identified using factor analysis of 17 components (including NO_2 to identify a traffic factor). Seven factors were identified for Manhattan and four factors for Sterling Forest.

Table 6-53 shows general ECG results over the exposure period for each location and identified source category. This is a semi-quantitative evaluation of the number of significant associations, given that there were 6 HR/HRV parameters (HR, SDNN, rMSSD, LF, HF, and LF/HF) analyzed over 4 different time periods (9:00 a.m.−2:00 p.m., 7:00 p.m.−10:00 p.m., 10:00 p.m.−1:00 a.m., 1:00 a.m.−3:00 a.m.) and three different lags (0, 1 and 2).

Table 6-53 Study results for identified source categories and occurrence of heart rate (HR) and heart rate variability (HRV) changes (Chen et al., 2010).

Location	Identified Source Categories	General HR and HRV Results
Manhattan	Incineration (Cu, Zn, Pb); Soil (Al, Si, Ca); Long-range transport (S, Se, Br, EC); Iron-manganese (Fe, Mn); Residual oil (V, Ni, EC); Traffic (EC, NO_2); Fireworks (K, Cu, Ba)	Residual oil had the most number of changes in HR/HRV (59) that were fairly evenly split across lags and time periods; long-range transport had the second most changes (45), with the majority at lag 0 and 1; traffic (30), FeMn (22) and incineration (21) were 3rd, 4th and 5th for number of changes; FeMn had the greatest number of responses on lag 0 and incineration had the greatest number of responses at lag 1; HR/HRV changes attributed to soil (14) were nearly all observed on lag 0; fireworks was associated with 1 HR/HRV change at lag 0 during the 7 PM-10 PM time period
Sterling Forest	Long-range transport (S, Se, Br, EC); Residual oil/traffic (V, BC); Ni-refinery (Ni, Cr, Fe); Soil (Al, Si, Ca)	Long range transport had double the number of occurrences of HR/HRV changes (34) compared to the next source factor, Ni refinery (17); the most numerous changes were at lag 0 and 1 for long-range transport; the most number of changes in HR/HRV for soil were observed at lag 1 (7 of 11); residual oil/traffic had the fewest counts of HR/HRV changes (3), all of which were observed at lag 0 in the 1 AM-4 AM time period

In looking at the two sites, long-range transport was associated with changes in cardiac function with both Manhattan and Sterling Forest CAPS. In contrast, the residual oil source factor was associated with the most number of changes in HR and HRV in Manhattan and the least in Sterling Forest (albeit it

was a combined residual oil and traffic source factor). The number of occurrences of HR and HRV changes associated with soil was similar in across the two sites, with the majority at lag 0 in Manhattan and lag 1 in Sterling Forest.

In another study of rats exposed to $PM_{2.5}$ CAPs in Detroit, for the summer months, 29 components were analyzed and PMF was used to investigate source factors (Rohr et al., 2011). Decreases in SDNN using 30-minute data in the summer were associated with 4 of 6 identified source factors - iron/steel manufacturing, sludge incinerator, cement/lime production and gasoline and diesel-powered vehicles. The strongest association was with the vehicle source factor and no association was observed with the refinery or secondary sulfate source factors. Similar to summer, 6 source factors were identified in winter. However, there were differences in that sludge incinerator source was only identified in summer and the iron/steel manufacturing was a part of the gasoline and diesel powered-vehicles and metal processing in winter. Increased HR in winter was associated with a refinery source factor and decreased HR was associated with the sludge incineration, cement/lime production and coal/secondary sulfate factors. For rMSSD, increases were associated with two factors - coal/secondary sulfate and gasoline and diesel-powered vehicles and iron/steel manufacturing.

In a study akin to (Rohr et al., 2011) that took place in Steubenville, OH, approximately 30 $PM_{2.5}$ components were measured and used to identify source factors using PMF (Kamal et al., 2011). Six factors were identified – coal/secondary, incineration, lead, metal coating/processing, mobile sources, and iron/steel manufacturing. There was a distinct difference in source contribution and ECG effects based on wind direction. Increased HR was associated with SW winds and the metal processing factor, whereas decreased HR was associated with NE winds and incineration, lead and iron/steel manufacturing factors. Decreased SDNN was associated with NE winds and the incineration factor and with SW winds and the metal factor. Increased rMSSD was only associated with combined winds and the iron/steel manufacturing factor.

6.2.18 Summary and Causality Determination

The evidence reviewed in the 2009 PM ISA provided the rationale to conclude that there is "a causal relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects" (U.S. EPA, 2009). Studies of mortality from cardiovascular causes provided the strongest evidence in support of this conclusion. While several studies included in the 2009 PM ISA reported associations between long-term PM_{10} exposure and morbidity outcomes such as post-MI CHF and DVT, studies of $PM_{2.5}$ were limited. One large prospective study of post-menopausal women reported an increased risk of cardiovascular events, including CHD and stroke, in association with long-term exposure to $PM_{2.5}$ (Miller et al., 2007). Cross-sectional analyses provided supporting evidence and experimental studies demonstrating enhanced atherosclerotic plaque development and inflammation following long-term exposures to $PM_{2.5}$ CAPs provided biological plausibility for the epidemiologic findings. In addition, a limited number of

toxicological studies reporting CAPs-induced effects on hypertension and vascular reactivity were drawn upon to support the causal conclusion. With respect to the current review, the evidence for the relationship between long-term exposure to $PM_{2.5}$ and cardiovascular effects is described below and summarized in Table 6-54, using the framework for causality determination described in the Preamble to the ISAs (U.S. EPA, 2015).

The studies of long-term exposure to $PM_{2.5}$ and cardiovascular mortality continue to provide strong evidence that there is a causal relationship between long-term exposure to $PM_{2.5}$ and cardiovascular effects. Results from recent U.S. and Canadian cohort studies demonstrate consistent, positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality (see Figure 6-19). Overall, studies reporting positive associations examine the relationship at varying spatial scales and employ different exposure assessment and statistical methods (Section 6.2.10). The studies were conducted in locations where mean annual average concentrations ranged from 4.08-17.9 $\mu g/m^3$. Generally, most of the $PM_{2.5}$ effect estimates relating long-term $PM_{2.5}$ exposure and cardiovascular mortality remained relatively unchanged or increased in copollutant models adjusted for ozone, NO_2, $PM_{10-2.5}$, or SO_2. In addition, most the results from analyses examining the C-R function for cardiovascular mortality supported a linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of $PM_{2.5}$ (Table 6-52).

The body of literature examining the relationship between long-term $PM_{2.5}$ exposure and cardiovascular morbidity has greatly expanded since the 2009 PM ISA, with positive associations reported in several cohorts. The findings from the WHI cohort of post-menopausal women (Miller et al., 2007), reporting associations of long-term $PM_{2.5}$ and coronary events, were strengthened through a subsequent analysis that considered potential confounding and modification by SES and applied enhanced exposure assessment methods (Chi et al., 2016a). Analyses of the NHS and CTS, which are both cohorts of women and include extensive data on covariates (i.e., hormone use, menopausal status and SES), were not entirely consistent with the WHI findings, however. Although the NHS cohort is comparable to WHI in that it is made of predominantly post-menopausal women, no associations with CHD or stroke were observed in this population (Hart et al., 2015b). An association with stroke, but not CHD, that was stronger among post-menopausal women was observed in the CTS (Lipsett et al., 2011). Several studies conducted among cardiovascular disease patient populations generally reported positive associations with MI (Hartiala et al., 2016; Tonne et al., 2015; Koton et al., 2013) and a sensitivity analysis of the NHS restricted to women with diabetes detected a positive association with CHD. Although the evidence is not consistent across the populations studied, heterogeneity is expected when the methods, or the underlying distribution of covariates vary across studies (Higgins, 2008).

Longitudinal change in measures of atherosclerosis in relation to long-term exposure to $PM_{2.5}$ add to the collective evidence base (Hartiala et al., 2016; Kaufman et al., 2016; Gan et al., 2014; Künzli et al., 2010). Findings were somewhat variable across cohorts and depended, in part, on the vascular bed in which atherosclerosis was evaluated. Kaufman et al. (2016) reported an association of $PM_{2.5}$ with CAC

among middle to older aged adults in the MESA study, while Dorans et al. (2016) reported no association in the Framingham Heart Study. Associations of long-term exposure to $PM_{2.5}$ with cIMT were not consistently observed across cohorts or between analyses of the same cohort with variable methods. Relationships between $PM_{2.5}$ and CIMT at younger ages were not observed. However, a recent toxicological study adds to similar evidence from the 2009 PM ISA by demonstrating increased plaque progression in $ApoE^{-/-}$ mice following long-term exposure to $PM_{2.5}$ collected from multiple locations across the U.S. (Section 6.2.4.2). Thus, this study provides direct evidence that long-term exposure to $PM_{2.5}$ may result in atherosclerotic plaque progression. This study is also coherent with those epidemiologic studies discussed above reporting positive associations between long-term exposure to $PM_{2.5}$ and indicators of atherosclerosis.

A small number of epidemiologic studies also report positive associations between long-term $PM_{2.5}$ exposure and HF (Section 6.2.5), blood pressure and hypertension (Section 6.2.7). These HF studies are in agreement with animal toxicological studies demonstrating decreased cardiac contractility and function, and increased coronary artery wall thickness following long-term $PM_{2.5}$ exposure (Section 6.2.5.2). Similarly, a limited number of animal toxicological studies demonstrating a relationship between long-term exposure to $PM_{2.5}$ and consistent increases in BP in rats and mice are coherent with epidemiologic studies reporting positive associations between long-term exposure to $PM_{2.5}$ and hypertension.

Longitudinal epidemiologic analyses also support the observation of positive associations with markers of systemic inflammation (Section 6.2.12), coagulation (Section 6.2.13), and endothelial dysfunction (Section 6.2.14). These results are in coherence with animal toxicological studies generally reporting increased markers of systemic inflammation and oxidative stress (Section 6.2.12.2), as well as with toxicological studies generally demonstrating endothelial dysfunction as evidenced by reduced vasodilation in response to acetylcholine (Section 6.2.14).

There is also consistent evidence from multiple, high-quality epidemiologic studies that long-term exposure to $PM_{2.5}$ is associated with mortality from cardiovascular causes. Associations with CHD, stroke and atherosclerosis progression were observed in several additional high-quality epidemiologic studies providing coherence with the mortality findings. Results from copollutant models generally support the independence of the $PM_{2.5}$ associations. Additional evidence of the direct effect of $PM_{2.5}$ on the cardiovascular system is provided by experimental studies in animals, which in part, demonstrate biologically plausible pathways by which long-term inhalation exposure to $PM_{2.5}$ could potentially result in outcomes such as CHD, stroke, CHF and cardiovascular mortality (Section 6.2.1). Taken together, these epidemiologic and experimental studies constitute strong evidence that **a causal relationship exists between long-term exposure to $PM_{2.5}$ and cardiovascular effects.**

Table 6-54 Summary of evidence for a causal relationship between long-term $PM_{2.5}$ exposure and cardiovascular effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Consistent epidemiologic evidence from multiple, high-quality studies at relevant $PM_{2.5}$ concentrations	Positive associations between long-term $PM_{2.5}$ exposure and cardiovascular mortality in U.S. and Canadian cohorts; positive associations persisted after adjustment for common confounders.	Section 6.2.10 Figure 6-19	Mean concentrations ranged from 4.08 $\mu g/m^3$ (CCHS) – 17.9 $\mu g/m^3$ CA Teachers
	Positive associations observed in studies examining varying spatial scales and across different exposure assessment and statistical methods.	Section 6.3.10.1	
Evidence from copollutant models generally supports an independent $PM_{2.5}$ association	Positive associations observed between long-term $PM_{2.5}$ exposure and cardiovascular mortality remain relatively unchanged after adjustment for copollutants. Correlations with ozone were generally moderate to high (0.49-0.73). When reported, correlations with SO_2, NO_2 and $PM_{10-2.5}$ ranged from weak to moderate (r = 0.25-0.55).	Section 6.3.10.25 Figure 6-21 Figure 6-22	
Epidemiologic evidence supports a linear no-threshold concentration response (C-R) relationship.	Majority of analyses support a linear, no-threshold relationship for cardiovascular mortality, especially at lower ambient concentrations of $PM_{2.5}$. Confidence in C-*R* relationship extends to 8 $\mu g/m^3$ in Harvard Six Cities study	Section 6.2.10 Lepeule et al. (2012)	
Inconsistent evidence from epidemiologic studies of CHD or stroke	High quality epidemiologic study reports association with coronary events, CHD and stroke (mortality and morbidity combined) among post-menopausal women that persist after adjustment for SES. Association with stroke but not CHD in the CA Teachers cohort No association with CHD or stroke in the NHS or HPFU	(Chi et al., 2016a; Miller et al., 2007) Lipsett et al. (2011) Puett et al. (2011) Hart et al. (2015b)	Mean: 13.4 $\mu g/m^3$ Mean: 15.6 $\mu g/m^3$ Mean: 17.8 $\mu g/m^3$ Mean: 13.4 $\mu g/m^3$

Table 6-54 (Continued): Summary of evidence indicating that a causal relationship exists between long-term $PM_{2.5}$ exposure and cardiovascular effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	$PM_{2.5}$ Concentrations Associated with Effects[c]
Generally consistent evidence of an association with CHD or stroke among those with preexisting disease	Consistent associations with MI in patient populations Association among women with diabetes in NHS	Hartiala et al. (2016) Tonne et al. (2015) Koton et al. (2013) Hart et al. (2015b)	Mean: 15.5 $\mu g/m^3$ Mean: 14.6 $\mu g/m^3$ Mean: 23.9 $\mu g/m^3$ Mean: 13.4 $\mu g/m^3$
Some but not all high quality epidemiologic studies provide evidence for effect of long-term $PM_{2.5}$ on CAC	Longitudinal change in CAC observed in MESA but not in Framingham Heart Offspring study	Kaufman et al. (2016) Dorans et al. (2016)	Mean: 14.2 $\mu g/m^3$ Median: 9.8 $\mu g/m^3$
Consistent evidence from animal toxicological studies at relevant $PM_{2.5}$ concentrations	Consistent changes in measures of impaired heart function and blood pressure Additional evidence of atherosclerosis, systemic inflammation, changes in endothelial function	Section 0 Section 6.2.4.2 Section 6.2.7.2 Section 6.2.12.2 Section 6.2.14.2	~85- 130 $\mu g/m^3$ See Tables in identified sections
Generally consistent evidence for biological plausibility of cardiovascular effects	Strong evidence for coherence of effects across scientific disciplines and biological plausibility for a range of cardiovascular effects in response to long-term $PM_{2.5}$ exposure. Includes evidence for impaired heart function, atherosclerosis, and increased blood pressure.	Section 6.2.1	

$PM_{2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 2.5 µm; PM_{10} = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm; $PM_{10-2.5}$ = particulate matter with a nominal aerodynamic diameter less than or equal to 10 µm and greater than a nominal diameter of 2.5 µm; SO_2 = sulfur dioxide.

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Tables I and II of the Preamble.

[b]Describes the key evidence and references contributing most heavily to causal determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the $PM_{2.5}$ concentrations with which the evidence is substantiated.

6.3 Short-Term $PM_{10-2.5}$ Exposure and Cardiovascular Effects

The 2009 PM ISA concluded that the available evidence for short-term $PM_{10-2.5}$ exposure and cardiovascular effects was "suggestive of a causal relationship." This conclusion was based on several epidemiologic studies reporting associations between short-term $PM_{10-2.5}$ exposure and cardiovascular

effects including ischemic heart disease (IHD) hospitalizations, supraventricular ectopy, and changes in heart rate variability (HRV). In addition, dust storm events resulting in high concentrations of crustal material were linked to increases in cardiovascular disease emergency department (ED) visits and hospital admissions. However, it was noted in the last review that there were concerns with respect to the potential for exposure measurement error in these epidemiologic studies because of the methods employed to estimate $PM_{10-2.5}$ concentrations. In addition, there was limited evidence of cardiovascular effects from the few experimental studies that examined short-term $PM_{10-2.5}$ exposures. Thus, in the last review, key uncertainties included the potential for exposure measurement error and biological plausibility of associations reported in epidemiologic studies.

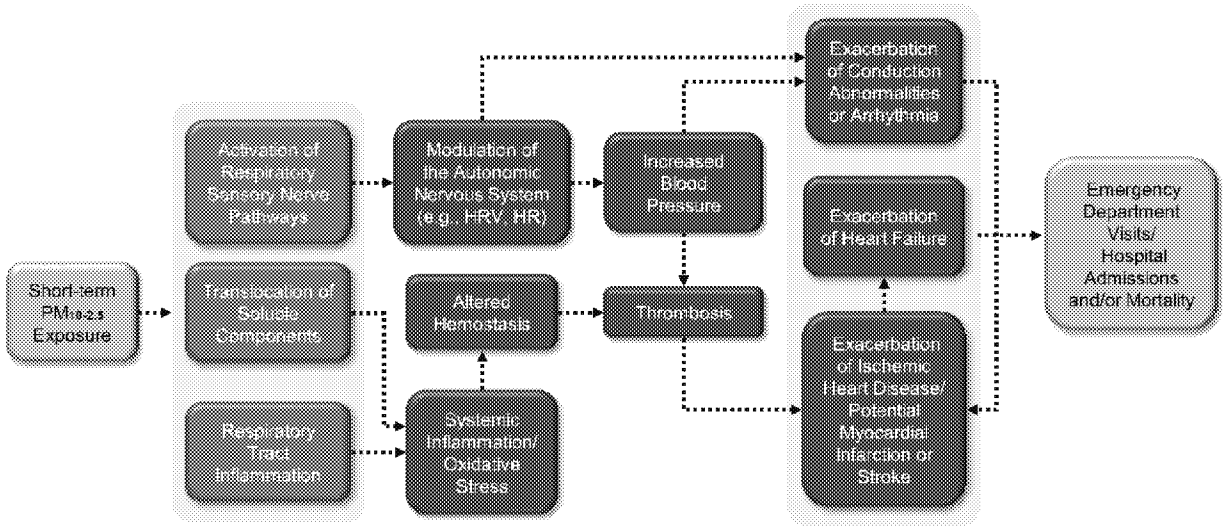
Evidence published since the completion of the 2009 PM ISA continues to be suggestive of a causal relationship between short-term exposures to $PM_{10-2.5}$ and cardiovascular effects. Since the publication of the 2009 PM ISA, there were a small number of epidemiologic studies reporting positive associations between exposure to $PM_{10-2.5}$ and IHD ED visits and hospital admissions. However, there is only limited evidence to suggest that these associations are independent of copollutant confounding. Similarly, there is only limited biological plausibility for IHD ED visits or hospital admissions from CHE, epidemiologic panel, and animal toxicological studies. Finally, similar to those studies evaluated in the 2009 PM ISA, the approaches used to estimate $PM_{10-2.5}$ concentrations continue to vary across studies leading to uncertainty regarding the extent to which exposure measurement error might be impacting the epidemiologic results.

The subsections below provide an evaluation of the most policy relevant scientific evidence relating-short-term $PM_{10-2.5}$ exposure to cardiovascular health effects. To clearly characterize and put this evidence into context, there is first a discussion of the biological plausibility of cardiovascular effects following short-term $PM_{10-2.5}$ exposure (Section 6.3.1). Following this discussion, the health evidence relating short-term $PM_{10-2.5}$ exposure and specific cardiovascular health outcomes is discussed in detail: ischemic heart disease and myocardial infarction (Section 6.3.2), heart failure and impaired heart function (Section 6.3.3) cardiac electrophysiology and arrhythmia (Section 6.3.4), cerebrovascular disease and stroke (Section 6.3.5), increased blood pressure and hypertension (Section 6.3.6), aggregated cardiovascular outcomes (Section 6.3.7), and cardiovascular-related mortality (Section 6.3.8). The evidence for an effect of $PM_{10-2.5}$ exposures on endpoints such as changes in heart rate variability (HRV) and endothelial function are then discussed (Section 6.3.9, Section 6.3.10, Section 6.3.11, and Section 6.3.12). Finally, considering the all of the information presented above, summary and causal determinations are presented (Section 6.3.13).

6.3.1 Biological Plausibility

This subsection describes the biological pathways that potentially underlie cardiovascular health effects resulting from short-term inhalation exposure to $PM_{10-2.5}$. Figure 6-30 graphically depicts these

proposed pathways as a continuum of pathophysiological responses—connected by arrows—that may ultimately lead to the apical cardiovascular events observed in epidemiologic studies. This discussion of "how" short-term exposure to $PM_{10-2.5}$ may lead these cardiovascular events also provides at least some biological plausibility for the epidemiologic results reported later in Section 6.3. In addition, most studies cited in this subsection are discussed in greater detail throughout Section 6.3.



Note: the boxes above represent the effects for which there is experimental or epidemiologic evidence, and the dotted arrows indicate a proposed relationship between those effects. Shading around multiple boxes denotes relationships between groups of upstream and downstream effects. Progression of effects is depicted from left to right and color coded (grey, exposure; green, initial event; blue, intermediate event; orange, apical event). Here, apical events generally reflect results of epidemiologic studies, which often observe effects at the population level. Epidemiologic evidence may also contribute to upstream boxes.

Figure 6-30 Potential biological pathways for cardiovascular effects following short-term exposure to $PM_{10-2.5}$.

When considering the available health evidence, plausible pathways connecting short-term exposure to $PM_{10-2.5}$ to the apical events reported in epidemiologic studies are proposed in Figure 6-30. The first pathway begins as respiratory tract inflammation leading to systemic inflammation.[64] The second pathway involves activation of sensory nerves in the respiratory tract that leads to modulation of the autonomic nervous system. Once these pathways are initiated, there is evidence from experimental and observational studies that short-term exposure to $PM_{10-2.5}$ may result in a series of pathophysiological

[64] It is also possible that soluble particle components can translocate directly into the circulatory system (Chapter 4) and lead to systemic inflammation, although the extent to which particle translocation occurs remains unclear.

responses that could lead to cardiovascular events such as ED visits and hospital admissions for IHD and HF, and ultimately mortality.

Short-term exposure to $PM_{10-2.5}$ may result in respiratory tract inflammation (Section 5.2). Inflammatory mediators such as cytokines produced in the respiratory tract may then enter into the circulatory system where they can cause distal pathophysiological responses and can contribute to overt cardiovascular disease (see Section 6.1.1). There is some evidence from a controlled human exposure study (Behbod et al., 2013) that following short-term exposure to $PM_{10-2.5}$, systemic inflammation may occur. Once in the circulation, inflammatory cytokines such as IL-6 can stimulate the liver to release coagulation factors that can alter hemostasis and increase the potential for thrombosis (see Section 6.1.1). It is therefore important to note that there is some evidence from a CHE (Graff et al., 2009) and an epidemiologic panel study (Huttunen et al., 2012) that following short-term exposure to $PM_{10-2.5}$, altered hemostasis may occur. Thus, the IHD and HF-related ED visit and hospital admission associations reported in epidemiologic studies are at least plausible through a pathway that includes thrombosis (Figure 6-30). This potential pathway could also plausibly contribute to the development of MI or stroke (Figure 6-30).

In addition to short-term $PM_{10-2.5}$ exposure potentially leading to worsening of cardiovascular disease through respiratory tract inflammation, there is also evidence that short-term exposure to $PM_{10-2.5}$ could potentially lead to worsening of cardiovascular disease through the activation of sensory nerves in the respiratory tract (CHAPTER 5). Sensory nerve activation can potentially result in modulation of the autonomic nervous system which may lead to changes in BP, conduction abnormalities, or arrhythmia (see Section 6.1.1). Thus, it is notable that there is a CHE study (Brook et al., 2014) that demonstrates autonomic nervous system modulation (as evidenced by changes in HRV and HR) following short-term $PM_{10-2.5}$ exposure. There is also evidence from CHE (Byrd et al., 2016; Zhong et al.; Brook et al., 2014; Bellavia et al., 2013), epidemiologic panel (Zhao et al., 2015) and animal toxicological (Aztatzi-Aguilar et al., 2015) studies that short-term exposure to $PM_{10-2.5}$ is associated with increases in BP. Similarly, there is evidence from epidemiologic panel studies for indicators of arrhythmia (Bartell et al., 2013; Hampel et al., 2010) following short-term $PM_{10-2.5}$ exposure. This is important given that increases in BP (e.g., through shear stress induced thrombosis) and arrhythmia may worsen IHD and set the stage for HF.

Taken together, there are plausible pathways by which short-term exposure to $PM_{10-2.5}$ may worsen IHD or HF as well as contribute to the development of MI or stroke (Figure 6-30). These proposed pathways also provide biological plausibility for ED visits and hospital admissions following short-term $PM_{10-2.5}$ exposure. That said, the evidence supporting most of the individual events in these pathways is quite limited. This information will be used to inform a causal determination, which is discussed later in the chapter (Section 6.3.13).

6.3.2 Ischemic Heart Disease and Myocardial Infarction

As noted above, (Section 6.1.2) IHD is characterized by reduced blood flow to the heart. The majority of IHD cases are caused by atherosclerosis (Section 6.2.4), which can result in the blockage of the coronary arteries and restrict of blood flow to the heart muscle. Also noted above (Section 6.1.2), an MI occurs as a consequence of IHD, resulting in insufficient blood flow to the heart that overwhelms myocardial repair mechanisms and leads to muscle tissue death. Additional information on IHD and MI can be found in Section 6.1.2.

As detailed below, recent studies add to existing evidence from the 2009 PM ISA that increases in $PM_{10-2.5}$ concentrations are associated with increases in ED visits and hospital admissions for IHD. However, results from copollutant models provide limited evidence that the observed associations are independent of other examined copollutants, including $PM_{2.5}$. Moreover, exposure measurement error remains an important uncertainty. There were no CHE or animal toxicological studies examining the relationship between short-term exposure to $PM_{10-2.5}$ and indicators of IHD or MI.

6.3.2.1 Emergency Department Visits and Hospital Admissions

The 2009 PM ISA reviewed a handful of studies that considered the association between $PM_{10-2.5}$ and IHD ED visits and hospital admissions that reported generally positive associations. A multicity study in France observed a 6.4% (95% CI: 1.6, 11.4%) increase in hospital admissions for IHD at lag 0-1 (Host et al., 2007). Associations were also recorded in single-city studies in Detroit (Ito, 2003) and Toronto (Burnett et al., 1999). On the other hand, one study in Atlanta observed no evidence of an association (Metzger et al., 2004). Additionally, one study examined $PM_{10-2.5}$ concentrations in relation to MI, and observed a positive but imprecise (i.e., wide 95% CI) association (Peters et al., 2001).

Several recent studies provide additional evidence for a positive association between short-term $PM_{10-2.5}$ exposure and IHD ED visits and HA. Specifically, $PM_{10-2.5}$ exposure was associated with IHD hospital admissions among U.S. Medicare beneficiaries in a multicity MCAPS study (Powell et al., 2015), as well as in single-city studies of IHD hospital admissions in Hong Kong, China and Kaohsiung, Taiwan (Chen et al., 2015b; Qiu et al., 2013). In the MCAPS study, $PM_{10-2.5}$ exposure was associated with a 0.74% (95% CI: 0.29, 1.20%) increase in hospital admissions for IHD on the same day (Powell et al., 2015). The association was unchanged in copollutant models adjusting for $PM_{2.5}$. Qiu et al. (2013) also observed a positive association, which persisted but lost precision after adjustment for $PM_{2.5}$. In Kaohsiung, Taiwan, Chen et al. (2015b) considered nearly 23,000 hospital admissions for IHD and reported positive associations on cool and warm days. The observed associations were generally robust to adjustment for NO_2, SO_2, CO, and O_3 in copollutant models. One additional important uncertainty across the available studies remains exposure measurement error for $PM_{10-2.5}$. All studies used an indirect measure of $PM_{10-2.5}$ (the difference between county- or area-averaged PM_{10} and $PM_{2.5}$ measurements or

the difference between concentrations measured at single PM_{10} and $PM_{2.5}$ monitors). Chen et al. (2015b) indicate the monitors were collocated, though it was unclear if these authors relied on the difference from collocated monitors before the spatial averaging was done, or if the spatial averaging of the PM_{10} and $PM_{2.5}$ monitors was done first, and then the difference was taken. Overall, it remains unclear how exposure measurement error may be affected by differing approaches for assigning $PM_{10-2.5}$ exposure in these studies (Section 3.3.1).

6.3.3 Heart Failure and Impaired Heart Function

As noted above (Section 6.1.3), HF refers to a set of conditions in which the heart's pumping action is weakened. In congestive heart failure (CHF), the flow of blood from the heart slows, failing to meet the oxygen demands of the body, and returning blood can back up, causing swelling or edema in the lungs or other tissues (typically in the legs and ankles). Additional information on HF can be found in Section 6.1.3.

As detailed below, recent studies add to existing evidence from the 2009 PM ISA that increases in $PM_{10-2.5}$ concentrations are associated with increases in ED visits and hospital admissions for HF. However, results from copollutant models provide limited evidence that the observed associations are independent of other examined copollutants, including $PM_{2.5}$. Moreover, exposure measurement error remains an important uncertainty. There were no CHE or animal toxicological studies examining the relationship between short-term exposure to $PM_{10-2.5}$ and indicators of HF included in the 2009 PM ISA.

6.3.3.1 Emergency Department Visits and Hospital Admissions

The 2009 PM ISA reviewed one study examining the association between $PM_{10-2.5}$ and ED visits and hospital admissions for heart failure. In the Atlanta-based SOPHIA study, Metzger et al. (2004) observed weak and imprecise positive associations between coarse PM concentrations and ED visits for congestive heart failure (CHF). Since the release of the 2009 PM ISA, few recent studies are available for review. In the 110-county national Medicare cohort (MCAPS) study, Powell et al. (2015) reported a 0.40% (95% CI: -0.06, 0.87%) increase in heart failure hospitalizations associated with $PM_{10-2.5}$ concentrations on the same day (measured by the difference of collocated PM_{10} and $PM_{2.5}$ monitors). The association was attenuated in magnitude and precision, but still positive, in a two-pollutant model adjusting for $PM_{2.5}$. In a much smaller study in Taipei, Taiwan, Chen et al. (2015b) also observed positive associations between $PM_{10-2.5}$ (measured by the difference of collocated PM_{10} and $PM_{2.5}$ monitors) and CHF hospitalizations on both warm and cold days. The associations were robust in copollutant models adjusting for SO_2, and attenuated but still positive in two-pollutant models adjusting for NO_2, CO, and O_3. Overall, recent studies provide limited evidence supporting an association between $PM_{10-2.5}$ and ED visits and hospital admissions for heart failure. Results from copollutant models also provide limited evidence

that the observed associations are independent of other examined copollutants; however, additional studies would be useful in providing more certainty regarding the nature of the association and addressing potential exposure measurement error from $PM_{10-2.5}$ measurements.

6.3.3.2 Toxicology Studies of Impaired Heart Function

There were no animal toxicological studies in the 2009 PM ISA (U.S. EPA, 2009) that examined the effect of short-term exposure to $PM_{10-2.5}$ on heart function. Since the publication of that document, Aztatzi-Aguilar et al. (2015) did not find an appreciable difference relative to control animals in expression of alpha skeletal actin (Acta1), or collagen-3 (Col3a1), two genes know to respond during pathological states of cardiac damage. Thus, this study does not provide evidence of potential decreases in heart function following short-term $PM_{10-2.5}$ exposure. More information on this recently published study can be found in Table 6-55 below.

Table 6-55 Study specific details from toxicological studies of short-term $PM_{10-2.5}$ exposure and impaired heart function.

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per treatment group	$PM_{10-2.5}$: 107 µg/m^3 collected from a high traffic and industrial area north of Mexico City in early summer. 5 h/day for 3 days. Animals were sacrificed 24 h after final exposure.	Acta1 and Col3a1 gene expression

d = day, h = hour, n = number, f = female, M = male, Acta1 = skeletal alpha-actin, Col3a1 = collagen Type 3 alpha

6.3.4 Cardiac Electrophysiology, Arrhythmia, and Cardiac Arrest

Experimental and epidemiologic panel studies typically use surface ECGs to measure electrical activity in the heart resulting from depolarization and repolarization of the atria and ventricles. The *P* wave of the ECG represents atrial depolarization, while the QRS represents ventricular depolarization and the T wave, ventricular repolarization. See Section 6.1.4 for more information on ECG, arrhythmia, and experimental measures of conduction abnormalities.

In the 2009 PM ISA, the evidence for arrhythmia related to short-term exposures to $PM_{10-2.5}$ was limited to a study reporting no associations between short-term $PM_{10-2.5}$ exposure and the risk of hospitalization for arrhythmia, and a panel studies demonstrating positive associations for ventricular arrhythmias. Since the 2009 PM ISA, there have been a few epidemiologic studies examining the

relationship between short-term PM 10-2.5 exposure and arrhythmia related HA. Although these studies generally show positive associations, uncertainties with respect to copollutant confounding and exposure measurement error remain. In addition, two panel epidemiologic studies only provide limited evidence of associations between short-term exposure to $PM_{10-2.5}$ and indicators of arrhythmia.

With respect to cardiac arrest, there were no studies included in the 2009 PM ISA and studies published since the last review are limited and inconsistent. That is, there are only a few studies that examined this endpoint, and the results of those few studies are not in agreement.

6.3.4.1 Emergency Department Visits and Hospital Admissions for Arrhythmia and Out-of-Hospital Cardiac Arrest

A number of studies based on administrative databases evaluate the association between short-term $PM_{10-2.5}$ concentrations and the risk of hospital admissions for cardiac arrhythmias (also known as dysrhythmias). In these studies, a primary discharge diagnosis of ICD-9 427 has typically been used to identify hospital admissions for cardiac arrhythmias. ICD-9 427 includes a heterogeneous group of arrhythmias including paroxysmal ventricular or supraventricular tachycardia, atrial fibrillation and flutter, ventricular fibrillation and flutter, cardiac arrest, premature beats, and sinoatrial node dysfunction.

As reported in the 2009 PM ISA, Halonen et al. (2009) did not observe a positive association between $PM_{10-2.5}$ and risk of hospital admissions for arrhythmias in Helsinki, Finland. Since the 2009 PM ISA, there have been few recent studies published on the association between $PM_{10-2.5}$ exposure and arrhythmia. In a large national Medicare cohort (MCAPS) study, Powell et al. (2015) found a positive association between $PM_{10-2.5}$ and arrhythmia-related hospital admissions (ERR: 0.94% [95% CI: 0.40, 1.48%] associated with $PM_{10-2.5}$ concentrations on the same day, measured by the difference of collocated PM_{10} and $PM_{2.5}$ monitors). The association was robust to adjustment for $PM_{2.5}$ in a two-pollutant model. In Kaohsiung, Taiwan, Chen et al. (2015b) reported positive associations between $PM_{10-2.5}$ (measured by the difference of collocated PM_{10} and $PM_{2.5}$ monitors) and hospital admissions for arrhythmias on cool days. In copollutant models, the observed association was robust to adjustment for SO_2, NO_2, and O_3, and attenuated but still positive after adjustment for CO.

6.3.4.1.1 Out-of-Hospital Cardiac Arrest

The majority of out-of-hospital cardiac arrests are due to cardiac arrhythmias. The 2009 PM ISA did not review any epidemiologic studies of ambient $PM_{10-2.5}$ concentrations and risk of OHCA. More recent evidence is limited and inconsistent. In two recent studies, Rosenthal et al. (2013) and Raza et al. (2014) did not observe positive associations between $PM_{10-2.5}$ (measured by the difference of collocated PM_{10} and $PM_{2.5}$ monitors) and OHCA in Helsinki, Finland and Stockholm, Sweden, respectively. In contrast, Dennekamp et al. (2010) and Wichmann et al. (2013) observed positive and imprecise

associations between $PM_{10-2.5}$ and OHCA. Dennekamp et al. (2010) reported a 1.7% (95% CI: -1.8, 5.3%) increase in hospital admissions on the same day in Melbourne, Australia, while Wichmann et al. (2013) observed a 9.0% (95% CI: -0.7, 19.5%) increase in hospital admissions at Lag 3 in Copenhagen, Denmark.

6.3.4.2 Panel Epidemiologic Studies for Arrhythmia and Conduction Abnormalities

The evidence for associations between arrhythmia and conduction abnormalities and $PM_{10-2.5}$ is very limited across the current review and in the 2009 PM ISA (U.S. EPA, 2009). Metzger et al. (2007) published a study demonstrating positive associations between ventricular arrhythmias and exposure to $PM_{10-2.5}$ in patients in Atlanta, GA, as described in the 2009 PM ISA (U.S. EPA, 2009). A recently published study by Bartell et al. (2013) used personal, size-fractionated PM measurements and found that 24-hour $PM_{10-2.5}$ was associated with ventricular tachyarrhythmia (RR = 1.20; 95% CI: 0.90, 1.59), but null associations were observed for 1-day (RR = 0.87; 95% CI: 0.71, 1.06) or 2-day lags (RR = 0.97; 95% CI: 0.66, 1.44). Hampel et al. (2010) reported positive associations between 24-47-hour average $PM_{10-2.5}$, determined using the difference method, with QTc (0.8%; 95% CI: 0.3%, 1.3%), but not for 0-23-hour averages or 3- to 5-day averages.

6.3.5 Cerebrovascular Disease and Stroke

Cerebrovascular disease typically includes conditions classified under ICD10 codes I60-I69 (ICD 9: 430-438) such as hemorrhagic stroke, cerebral infarction (i.e., ischemic stroke) and occlusion of the pre-cerebral and cerebral arteries. Ischemic stroke results from an obstruction within a blood vessel that supplies oxygen to the brain, potentially leading to infarction, and accounts for the majority of all strokes (Goldberger et al., 2008). Hemorrhagic stroke is less common but results to a disproportionate amount of fatalities. Additional information on cerebrovascular disease and stroke can be found in Section 6.1.5.

The 2009 PM ISA did not review any epidemiologic studies of short-term exposure to $PM_{10-2.5}$ emergency department visits and hospital admissions visits for cerebrovascular disease (CBVD). In the current review, a limited number of studies provide inconsistent evidence regarding the presence of an association. Moreover, there are uncertainties with respect to copollutant confounding and exposure measurement error.

6.3.5.1 Emergency Department Visits and Hospital Admissions

A limited number of recent studies provide inconsistent evidence regarding the presence of an association between short-term $PM_{10-2.5}$ exposure and ED visits and hospital admissions for CBVD.

Studies in Rome, Italy (Alessandrini et al., 2013) and Kaohsiung, Taiwan (Chen et al., 2015b) reported some evidence of an association between short-term $PM_{10-2.5}$ concentrations and ED visits and hospital admissions for CBVD. Alessandrini et al. (2013) considered 26,557 hospital admissions for CBVD in the context of Saharan dust outbreaks, and observed a 1.6% (95% CI: -0.6, 3.8%) increase in risk of hospital admissions associated with $PM_{10-2.5}$ concentrations measured on the same day. The association was larger in magnitude, but less precise (i.e., wide 95% CIs) on days with high Saharan dust levels, though effect measure modification by Saharan dust level was not statistically significant. Chen et al. (2015b) also evaluated approximately 25,000 hospitalizations for CBVD and reported associations with $PM_{10-2.5}$ concentrations on both warm and cool days, with a larger magnitude association observed on warm days. The observed association on warm days was robust to adjustment for SO_2 and O_3, and attenuated but still positive after adjustment for NO_2 and CO in copollutant models. Additional studies conducted in China reported inconsistent evidence of an association (Huang et al., 2016; Qiu et al., 2013). Huang et al. (2016) reported a positive association between $PM_{10-2.5}$ concentrations and stroke ED visits (lag 0) when adjusted for CO, or NO_2 in Beijing, China. Additionally, when examining ischemic and hemorrhagic stroke subtypes Huang et al. (2016) observed positive associations at lag 0, while associations were attenuated but still positive, or null, at longer lag periods (lag 1 to lag 3). Furthermore, the authors also reported consistently stronger associations across lag periods for ED visits on days when the temperature was greater than 13.5°C. In contrast to the studies in Rome, Kaohsiung and Beijing, a study of over 100,000 ED visits in Hong Kong, China reported a null association between CBVD hospital admissions and $PM_{10-2.5}$ concentrations (Qiu et al., 2013). One additional important uncertainty across the available studies remains the use of an indirect measure of $PM_{10-2.5}$ and the potential for exposure measurement error for $PM_{10-2.5}$ (Section 3.3.1). Overall, there remains limited and inconsistent evidence of an association between $PM_{10-2.5}$ and CBVD.

6.3.6 Blood Pressure and Hypertension

High blood pressure results in the increased force on the artery walls and can damage the blood vessels and increase risk for cardiovascular disease and stroke. Hypertension typically develops over years and is the clinically relevant blood pressure outcome, defined as SBP above 140 mm hg or DBP above 90 mm hg. That being said, small population-level changes in blood pressure, even in the absence of clinical hypertension, can have large effects on clinical outcome prevalence (Rose, 1985). Additional information on blood pressure and hypertension can be found in Section 6.1.6 and Section 6.2.7.

There was a single epidemiologic panel study in the 2009 PM ISA finding a decrease in SBP following short-term $PM_{10-2.5}$ exposure (U.S. EPA, 2009). Since the publication of the 2009 PM ISA, an epidemiologic panel study and a few CHE studies provide some evidence of an effect of short-term PM 10-2.5 exposure on measurements of blood pressure. In addition, an animal toxicological study also reported that short-term exposure to $PM_{10-2.5}$ could result in changes in the blood pressure regulating renin-angiotensin system at the mRNA level. Thus, studies published since the completion of the 2009

PM ISA provide some additional evidence that short-term exposure to $PM_{10-2.5}$ may result in changes in BP.

6.3.6.1 Panel Epidemiologic Studies of Changes in Blood Pressure (BP)

For the 2009 PM ISA (U.S. EPA, 2009), a single study was evaluated (Ebelt et al., 2005) that examined the association between BP and $PM_{10-2.5}$. Ebelt et al. (2005) reported decreases in SBP relative to $PM_{10-2.5}$ determined using the subtraction method. A recent panel study examined cardiovascular effects among people with diabetes and short-term exposure to $PM_{10-2.5}$ (calculated by the subtraction method) in Shanghai where daily averages of $PM_{2.5}$ and $PM_{10-2.5}$ during the study period were 60 ug/m^3 and 19 ug/m^3, respectively. Specific lags of 0-2, 3-6, 7-12, and 13-24 hours were positively associated with DBP but associations with SBP and PP across lags were null (Zhao et al., 2015).

6.3.6.2 Controlled Human Exposure Studies of Changes in Blood Pressure (BP)

In the 2009 PM ISA (U.S. EPA, 2009), there were no CHE studies that examined the effect of $PM_{10-2.5}$ on blood pressure. Since the last review, there have been studies examining changes in blood pressure in response to short-term exposure to urban (Byrd et al., 2016; Bellavia et al., 2013), as well as rural (Brook et al., 2014) $PM_{10-2.5}$.

In response to urban $PM_{10-2.5}$, Bellavia et al. (2013) reported small, but significant ($p = 0.03$) elevations in SBP, but not DBP. These results are generally in agreement with an additional study of urban $PM_{10-2.5}$. Byrd et al. (2016) found exposure to urban $PM_{10-2.5}$ resulted in small (~1-3 mm hg), increases in SBP ($p < 0.001$), DBP ($p < 0.001$), and pulse pressure ($p = 0.03$) when compared to FA.

Changes in blood pressure were also demonstrated in a CHE study of rural $PM_{10-2.5}$. Brook et al. (2014) reported an increase in both SBP ($p = 0.021$) and DBP ($p = 0.05$) during the exposure period when compared to FA (results were reiterated in (Morishita et al., 2015b)). In addition, pooled blood pressure results from (Brook et al., 2014)and (Byrd et al., 2016) showed that changes in blood pressure in response to urban $PM_{10-2.5}$ were on average significantly greater throughout $PM_{10-2.5}$ exposure than those changes observed throughout the exposure to rural $PM_{10-2.5}$ (Byrd et al., 2016) ($p < 0.001$).

The CHE studies presented in the current ISA provide evidence of a small, but reproducible effect of urban and rural $PM_{10-2.5}$ exposure on BP elevation in healthy adults. Biological components present in PM may at least partially account for changes in BP. That is, Zhong et al. (2015) examined whether PM effects on BP were associated with endotoxin and β-1,3-d-glucan present in PM. After adjusting for total exposure mass, results indicated endotoxin was associated with increases in SBP 30-minutes post exposure, and DBP for up to 20 hours post exposure. β-1,3-d-glucan was only associated with an increase

in DBP 30 minutes post exposure. Finally, increases in BP could also be associated with hypomethylation. Bellavia et al. (2013) found Toll Like Receptor 4 (TLR4) hypomethylation (which can be a marker for increased inflammation) in response to $PM_{10-2.5}$ CAP exposure and an association between TLR4 hypomethylation and increases in SBP and DBP. More information on studies published since the 2009 ISA can be found in Table 6-56 below.

Table 6-56 Study-specific details from controlled human exposure (CHE) studies of short-term $PM_{10-2.5}$ exposure and blood pressure (BP).

Study	Population	Exposure Details (Concentration; Duration)	Endpoints Examined
Bellavia et al. (2013)	Healthy adults n = 8 M, 7 F 18-60 yr old 27.7 ± NA	~200 µg/m^3 $PM_{10-2.5}$ for 130 min at rest PM collected from a busy street in Toronto, Canada	BP: 10 min pre, 5 min post DNA methylation: 1 h post
Byrd et al. (2016)	Healthy adults 20 M, 9 F; 18-50 yrs 30 ± 8.2,	164.2 ± 80.4 µg/m^3 $PM_{10-2.5}$ CAP for 2 h CAP from urban Dearborn, MI	BP: every 7 min during exposure, post, 2 h post Vascular function: post, 2 h post
Brook et al. (2014)	Healthy adults n = 16 M, 16 F; 18-46 yr 25.9 ± 6.6,	76.2 ± 51.5 µg/m^3 $PM_{10-2.5}$ for 2 h CAPs from rural Dexter, MI	BP: every 10 min during exposure, post, and 2 h post
Morishita et al. (2015b)	Healthy adults n = 16 M, 16 F; 18-46 yr 25.9 ± 6.6	76.2 ± 51.5 µg/m^3 $PM_{10-2.5}$ CAP for 2 h CAP from rural Dexter, MI	Relationship between $PM_{10-2.5}$ components and changes in BP
Zhong et al. (2015)	Healthy adults n = 23 M, 27 F; 18-60 yr	Endotoxin and B-1,3-d-glucan associated with 200 µg/m^3 $PM_{10-2.5}$ CAP exposure for 130 min at rest CAP collected from a heavy-traffic 4-lane street in Toronto	BP: pre, 0.5 h and 20 h post

Note: SD = standard deviation, M = male, F = female, n = number, h = hour, yr = year, CAP = concentrated ambient particle, BP = blood pressure.

6.3.6.3 Toxicology Studies of Changes in Blood Pressure (BP)

There were no animal toxicological studies in the 2009 PM ISA examining the effect of $PM_{10-2.5}$ CAP exposure on measures of BP. Since the publication of that document, Aztatzi-Aguilar et al. (2015) exposed rats to $PM_{10-2.5}$ and reported that Ace and B1r, but not At1r mRNA levels in the heart were increased ($p < 0.05$). Thus, there is limited evidence at the mRNA level that exposure to $PM_{10-2.5}$ can result in changes to the renin-angiotensin system which could then, effect blood pressure. More information on this study can be found in Table 6-57 below.

Table 6-57 Study specific details from toxicological studies of short-term $PM_{10-2.5}$ exposure and blood pressure (BP).

Study	Study Population	Exposure Details	Endpoints Examined
(Aztatzi-Aguilar et al., 2015)	Adult Sprague-Dawley rats, M, n = 4 per treatment group	Inhalation of 107 μg/m^3 $PM_{10-2.5}$ for 5 h/day for 3 days	angiotensin and bradykinin system gene expression

Notes: n = number, h = hour, d = day, M = male

6.3.7 Emergency Department Visits and Hospital Admission Studies of Cardiovascular-Related Effects

Many epidemiologic studies consider the composite endpoint of ED visits and hospital admissions for all cardiovascular diseases, including diseases of the circulatory system. This endpoint generally encompasses ED visits and hospital admissions for ischemic heart disease, MI, PVD, heart failure, arrhythmia, CBVD and stroke, and diseases of pulmonary circulation. A smaller body of studies examines the endpoint of cardiac diseases, a subset of CVD that specifically excludes hospitalizations for cerebrovascular disease, peripheral vascular disease, and other circulatory diseases not involving the heart or coronary circulation. The 2009 PM ISA reviewed a limited number of studies on $PM_{10-2.5}$ and CVD ED visits and HA. In 108 U.S. counties with collocated PM_{10} and $PM_{2.5}$ monitors, Peng et al. (2008) reported a 0.8% (95%: 0.6, 1.0%) increase in risk of CVD hospital admissions among Medicare beneficiaries associated with $PM_{10-2.5}$ concentrations on the same day. A positive association was also observed in six French cities, but the association was much less precise (Host et al., 2008). Tolbert et al. (2007) did not find evidence of an association between $PM_{10-2.5}$ exposure and CVD ED visits and hospital admissions in Atlanta, Georgia. Recent multicity studies focus on overall CVD visits and provide some evidence that $PM_{10-2.5}$ may be associated with increased risk of cardiovascular-related HA, while results from single-city studies are inconsistent (Table 6-58).